CANCER RESEARCH

A MONTHLY JOURNAL OF ARTICLES AND ABSTRACTS REPORTING CANCER RESEARCH

VOLUME 6 SEPTEMBER, 1946 NUMBER 9

The Pathologic Effects of an Instantaneous Dose of Radiation*†

Capt. Shields Warren (MC) USNR

(Received for publication April 2, 1946)

The distinctive feature of the atomic bomb is the large amount of radiant energy that it produces. While this energy covers a wide range of the electromagnetic spectrum, its chief physiologic and pathologic effects may be divided into two groups: first, the effects of heat, producing primary thermal injury of the flash burn type, and secondary thermal injuries due to induced fires; second, the effects of short-wave radiation and neutrons, paralleling closely the effects familiar to us from the experimental studies of the biologic effects of x-rays. This radiant energy was produced in an instant. Security prevents statement as to the exact duration of time.

Of course, combined with and modifying and obscuring these effects are the more usual effects of the conventional types of bomb. Chief among these is air blast injury, almost always secondary, due to flying debris or impact against fixed structures.

In our studies of the atomic bomb effects at Nagasaki and Hiroshima, which were carried on under the direction of the Naval Medical Research Institute and the Naval Technical Mission to Japan, we concentrated particularly on the injuries due to radiation. For security reasons the type and quantity of this radiation cannot be discussed. Suffice it to say that radiation effects ranging from lethal to minimal were observed. We were very fortunate in our study to have the collaboration of the investigating group from the Manhattan District under Colonel Stafford L. Warren and the Joint U. S. Army Imperial Japanese Government Atomic Bomb Commission under Colonel A. W. Oughterson.

* This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the U. S. Navy. The opinions and views set forth in this article are those of the writer and are not to be considered as reflecting the policies of the Navy Department.

† Presidential address delivered at the 37th meeting of the American Association for Cancer Research, Inc., at Atlantic City, New Jersey, March 11, 1946.

The more conventional types of injury encountered we will mention briefly. The blast was highly destructive not only to the Japanese type of building, which is of flimsy wood with a heavy tile roof, but to modern steel factory construction as well. Since the Japanese buildings of concrete construction were earthquake-proof they are much more heavily reinforced and much more soundly built than most of our buildings.

The destructive effect of the blast was centrifugal except at the hypocenter (the projection of the true center on the ground) where it was essentially vertical. Consequently, some poles and trees stood at the hypocenter, although extensively leveled elsewhere. The importance of streamlining in resisting blast was well shown by factory smoke stacks, the great majority of which stood.

Medically, the air blast effects were chiefly of secondary type, fractures and rupture of viscera from impact of debris. Great numbers of persons were pinned beneath the heavy tile roofs of the Japanese houses as they collapsed, and were crushed or trapped.

The thermal injury was very striking in the immediacy of its effect and of its passing. Thus clothes, wisps of hair, or even the shadow of an arm across the body sufficed to protect. The intensity of the heat and the instantaneous character of the flash is well brought out by finding the profile of blades of grass in relief against the charred background of a board bunker where the intense but instantaneous radiant heat burned the wood before the grass had time to wave or wither. Many of the flash burns were of second or third degree. Their treatment was so inadequate that serious contractures developed in the survivors.

Of course with the sweep of fire that fed on the shattered wooden buildings, many secondary burns, from fatal to minor, were received by those trapped in the region, as well as by those attempting salvage or rescue.

As we studied our patients it became apparent that

there was no segregation of types of injury among them, but that an individual might well be suffering from blast effect, thermal injury and radiation injury simultaneously. Of the 80,000 people who died at Hiroshima and 45,000 that died at Nagasaki, it is very difficult to say what proportion were killed by one or another type of energy. Our primary interest is in those persons who died as a result of short-wave or neutron irradiation. Since the biologic responses to these different types of ionizing radiation are essentially similar, they will be considered *en masse*.

The characteristic clinical course of those persons primarily suffering from radiation injury as result of the atomic bomb explosions may be divided into two stages. The immediate effects were manifested as weakness, malaise, fever and often death, and appeared usually within 48 hours, while the delayed effects manifested themselves in a variety of ways.

Unfortunately, the disorganization of the Japanese was so great that no adequate material exists to determine the exact nature of immediate effects. We may assume, however, that they parallel experimentally induced changes in animals and represent the syndrome of radiation sickness carried to an extreme degree. We may assume that there is little morphologic evidence other than leukopenia and loss of adrenal lipoid.

Our material on the delayed effects is much better. When one considers that most of these cases received total body radiation it becomes obvious that the chance of survival with a dose equivalent to 500 r of conventional x-ray radiation would be extremely unlikely. Consequently we must look for effects in those tissues that are known to be particularly radiosensitive. These are, of course, the blood, hematopoietic and lymphoid tissues (Fig. 1), the gonads; sensitive to appreciably lesser degree are the hair follicles. Of course many of the patients showed evidences of injury to the total organism of the radiation sickness type. In this group in addition to weakness, anorexia and weight loss, diarrhea was a prominent feature. Owing to the fact that the hygiene of the region was totally disrupted and both bacillary and amoebic dysenteries were prevalent, it was extremely difficult to determine the cause of this diarrhea.

We received excellent cooperation from the Japanese authorities in studying survivors. Over 800 were hospitalized by our group at the Omura Naval Hospital, and about 13,000 were made available to us for a casualty survey.

It was easy, in the cities and villages around Nagasaki and Hiroshima, to pick out the irradiated refugees by the characteristic flash burns which they presented and by the not infrequent occurrence of epilation (Fig. 2). When we left in late December, over four months after the bombing, some degree of regeneration of new downy hair was beginning to appear in a fair number of the epilated cases. Scalp hair was lost while that of eyebrows, beard, axillae and pubis persisted.

The effect on the blood can be readily followed by clinical manifestation as well as from a laboratory standpoint. There were three chief groups of symptom complexes due to damage to hematopoietic tissue. While the groups overlapped to some degree they were quite distinctive. The first was the leukopenic group in which infection and particularly Ludwig's angina was the outstanding manifestation. The great bulk of leukopenic deaths occurred during the first three weeks following the bombing. Judging from the studies of Japanese investigators, the leukocytes in the circulating blood were destroyed at the same time that the hematopoietic tissue was damaged, so that white blood cell counts as low as 200 per cu. mm. were found in the first few days.

From 3 to 5 weeks after the bombing a considerable number of hemorrhagic deaths occurred, associated with the thrombocytopenia induced by radiation damage to the megakaryocytes of the bone marrow. Although we have no data, it is fair to assume that the absence of hemorrhagic deaths in the early days suggests that the blood platelets in the circulation were not destroyed by the radiation and only as a low point was reached as result of deficiency in blood did hemorrhagic manifestation occur. These ranged from extensive ecchymoses to purpuric patches and small petechiae. Some cases had massive hemorrhages from various body orifices. At autopsy it was not infrequent to find hemorrhage filling the pelvis of the kidney; multiple mucosal hemorrhages of the stomach or elsewhere in the gastrointestinal tract; multiple diffuse hemorrhages in the meninges or even in cerebral substance.

Those with serious bone marrow damage who weathered the first few weeks showed later anemic manifestations with red blood cell counts in some instances dropping to one million or below. The bone marrow as shown by sternal marrow biopsy frequently was extremely hyperplastic, while others were aplastic (Fig. 3). In relation to the aplastic group there was one point of interest. We commonly think of red marrow as being actively hematopoietic in contrast to the yellow fatty marrow. In many of these cases the aplastic marrow was red but its redness was due only to sinusoidal hyperemia and there was no appreciable formation of blood elements. At times the marrow was so depleted that little but reticulo-endothelial cells appeared.

The gonadal effect was much more prominent in case of the testis than of the ovary as would be suspected. Although a random sample of high school girls who previously had been menstruating regularly

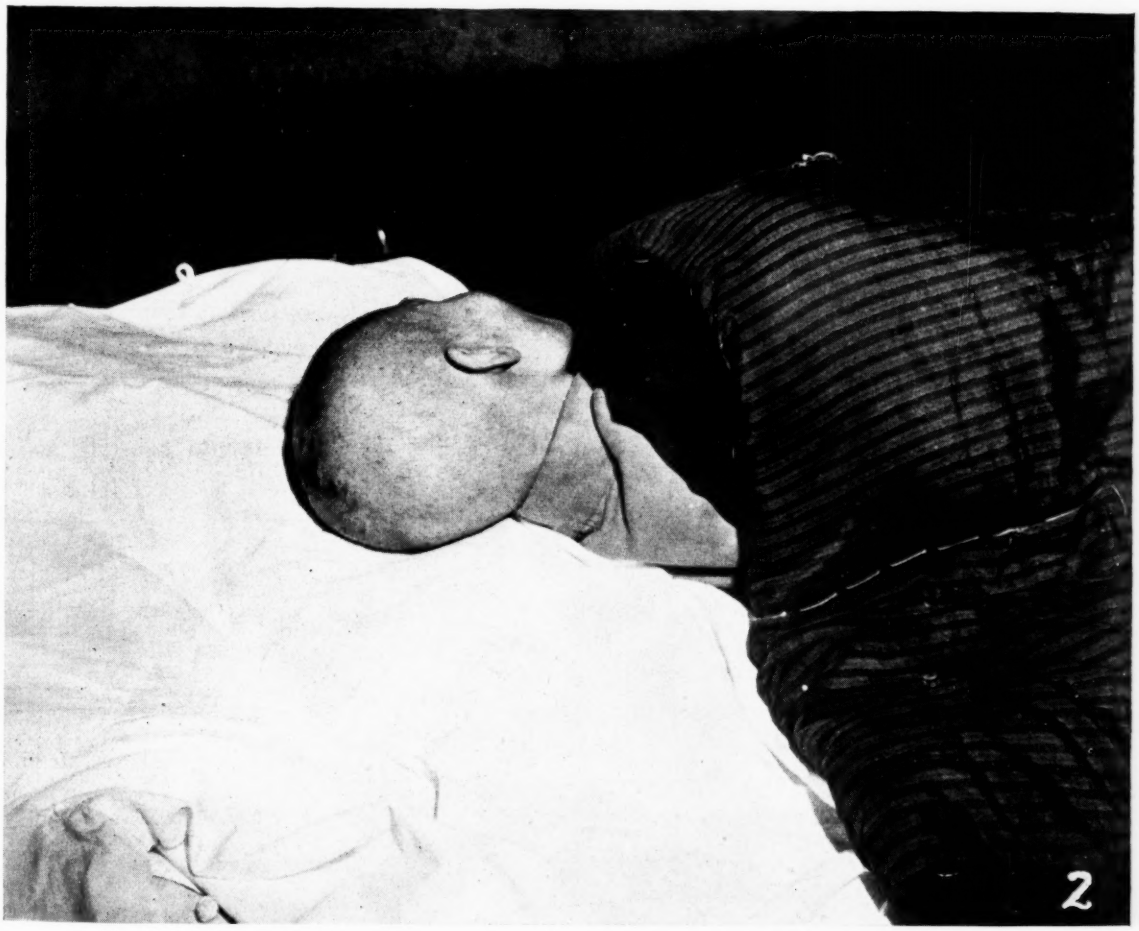
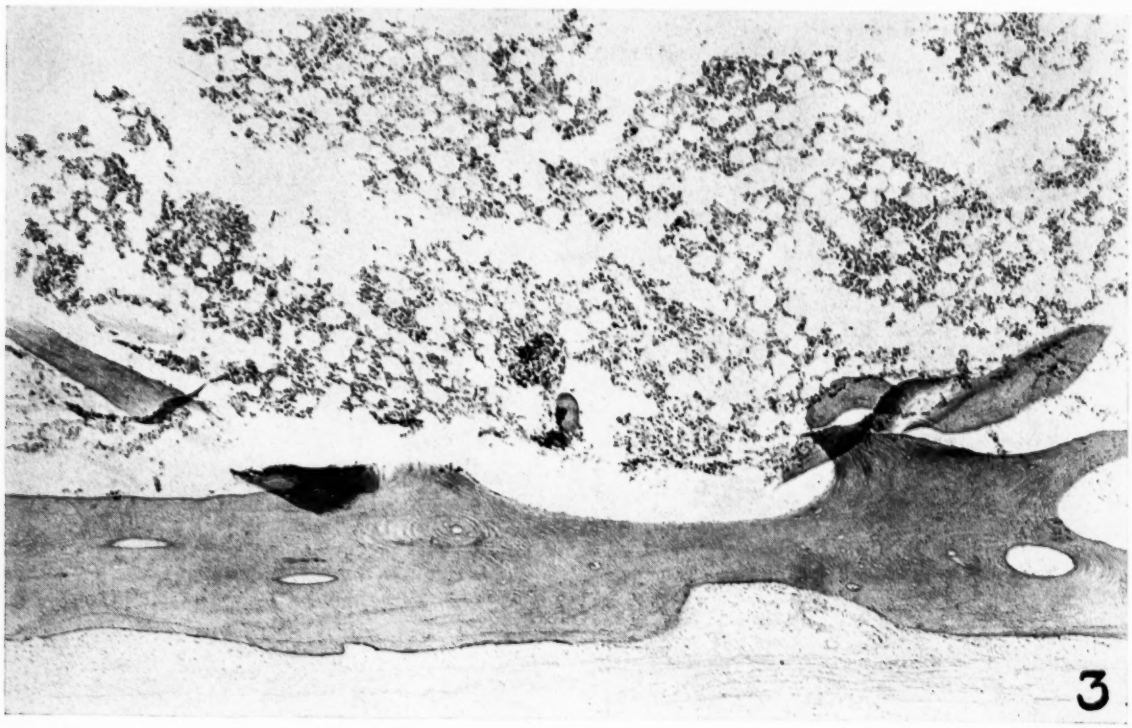


FIG. 1.—Spleen showing atrophy of lymphoid tissue. Hematoxylin-eosin stain. Mag. × 35.
FIG. 2.—Epilation following atomic bomb explosion at Nagasaki. Official U. S. Navy photograph.



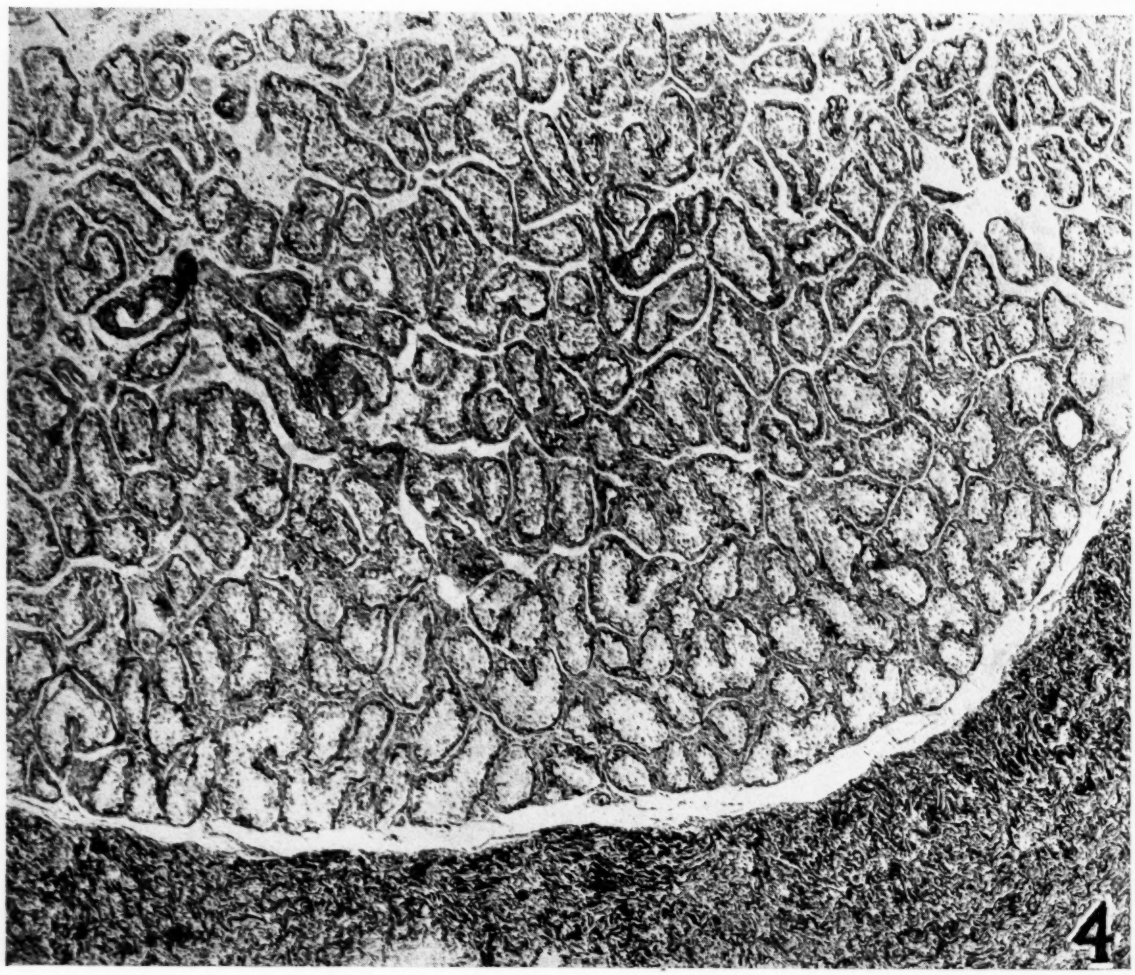


FIG. 3.—Partial regeneration of hematopoietic bone marrow. Hematoxylin-eosin stain. Mag. × 50.
FIG. 4.—Testis showing atrophy of germinal epithelium. Hematoxylin-eosin stain. Mag. × 50.

showed suppression of menstruation in a considerable number, the probability of psychic shock and malnutrition must be weighed as well as direct ovarian effect. Ova were present in ovaries in many cases; only occasionally in women of the child-bearing age did atrophy occur. However, it was relatively infrequent to find a recent corpus hemorrhagicum or corpus luteum. In the testis, on the other hand, in those individuals who had been exposed to appreciable amounts of radiation, atrophy of the germinal epithelium was striking (Fig. 4). Spermatogenesis was suppressed and frequently the tubules were represented only by Sertoli cells and thickened membranes. The interstitial cells were not damaged.

The question of injury from residual radioactivity was of major importance. We were fortunate in locating a number of persons who had entered the bombed areas soon after the explosion and had remained there. None showed any deleterious effects.

In the forthcoming Crossroads Operation vital biologic data will be obtained, data that are essential to close in the gaps in our knowledge that exists as to the pathology in the periods shortly after the explosions. The total disorganization of the Japanese medical and reserve services following the bombings resulted in almost complete absence of information in the early phases.

We were also interested in therapy. The treatment given by the Japanese was utterly inadequate, as were their hospital facilities. Blood transfusions were not used. Little more than supportive treatment was given. Burns were treated with oily dressings or picric acid. Repeated blood transfusions, penicillin to control infection during the leukopenic period should have materially reduced the number of deaths.

The hematopoietic tissue attempts to regenerate, sometimes to such a degree that a pseudoleukemic pattern appears in the sternal marrow biopsy. Interestingly enough, one case of monocytic leukemia developed in a young man in November, only a few weeks after he had been discharged from a Japanese hospital where he was under treatment for leukopenia and anemia.

I am quite sure it will be necessary to follow the populations of Hiroshima and Nagasaki for many years to determine the long range results in production of blood dyscrasias, in alteration of resistance to disease and in genetic changes induced by this instantaneous dose of radiation.

The Carcinogenic Activity of Some New Derivatives of Aromatic Hydrocarbons

II. Compounds Related to 1,2-Benzanthracene*†

Charles E. Dunlap, M.D.,** and Shields Warren, M.D.

(From the Laboratory of Pathology, Harvard Cancer Commission, and the Department of Pathology, Harvard Medical School, Boston 14, Massachusetts)

(Received for publication March 13, 1943)

INTRODUCTION

In 1939 a program of investigation was undertaken in collaboration with Professor Louis F. Fieser and his associates at Harvard University, directed toward a further study of the chemistry of artificial carcinogenesis. The main task was a biological testing for carcinogenicity of a number of new hydrocarbon derivatives synthesized by Dr. Fieser's group. Although the chief purpose of this paper is to present data on the carcinogenic tests of compounds related to 1,2-benzanthracene, some discussion of the problem as a whole is necessary in order to relate this report to those that will be published subsequently.

In spite of the enormous amount of work that has been done on synthetic carcinogenic agents, and the testing of well over 700 compounds, it is still impossible to formulate any generalization that defines the features of chemical structure necessary for carcinogenic action. It does appear that substituents in the 9-, 10-, 5-, and 6- positions of 1,2-benzanthracene are more likely to render the molecule active than if placed elsewhere in the molecule, and that hydrogenation of the aromatic rings or the substitution of large radicals reduces activity; however, none of these generalizations is definitive. Neither physical characteristics such as atomic weight, melting point, solubility, and surface tension effect nor the known chemical reactivity of the various compounds (15) has yet been successfully correlated with carcinogenic activity. Nevertheless, the striking changes in activity that follow the slightest alteration of structure imply a high degree of chemical specificity in the process of chemical carcinogenesis. This makes it appear profitable to continue the search for some common denominator among carcinogenic chemicals that will set the active ones apart from their inactive relatives, and perhaps provide a clue to the initial step in the biological process of artificial tumor induction.

In order to define the problem more clearly it seemed desirable to determine the carcinogenic activity of a considerable number of new chemical compounds, synthesized by Dr. Fieser and his group and chosen by them as those most likely to throw some light on the nature of the structural modifications that would enhance, diminish, or destroy carcinogenic activity.

Several lines of thought influenced the choice of these substances, and a number of new syntheses were evolved in order to obtain them. For example, there are 12 possible isomeric forms of monomethyl 1,2-benzanthracene, all of which have been synthesized and tested. The results have shown that carcinogenic activity is dependent to a remarkable degree on the position of the substituted methyl group in the molecule. A number of our new compounds represent members of other series of isomers, such as the dimethyl benzanthracenes and the monomethyl benzpyrenes. The results obtained with these compounds should help to define more clearly the importance of the position of substitution as it affects carcinogenic potency.

Not only the position of substitution but the nature of the substituent group has been shown to influence carcinogenic action. In general, a progressive loss of potency follows an increase in the size or complexity of the substituent. Thus 10-methyl-1,2-benzanthracene is very active, the 10-ethyl derivative is moderately so, and the 10-propyl is inactive. Substitution of functional groups usually reduces activity. We have tested a number of compounds substituted at the same molecular position but with different radicals, as, for example, the group of 5-substituted benzpyrene derivatives (13).

* This investigation was aided by a grant from the Jane Coffin Childs Memorial Fund for Cancer Research.

† The compounds utilized in these experiments were selected and synthesized by Professor L. F. Fieser and his associates in the Department of Chemistry, Harvard University.

** Now at the School of Medicine, Tulane University of Louisiana, New Orleans, La.

Several of the new compounds have structural features common to two or more of the established carcinogens. Thus 1′,9-methylene-10-methyl-1,2-benzanthracene may be considered either as a substitution product of 10-methyl-1,2-benzanthracene or as a derivative of 10-methyl-3,4-benzpyrene, in which a 5-carbon ring has replaced one of the aromatic 6-carbon rings. Other compounds were tested that contain only a portion of an established carcinogenic nucleus; for example, the chrysene derivatives reported in a previous communication (12) lack only one benzene ring to complete the structure of benzpyrene. Active tumor production, particularly with 5-methylchrysene, shows that some simplification of the benzpyrene nucleus is possible without complete loss of carcinogenic action.

A peculiar group of carcinogenic agents is known that selectively affect the liver regardless of the route of administration. Although differing considerably in structure among themselves, one feature common to this group is the presence of nitrogen in the molecule. Many of the compounds bear no structural similarity to the carcinogenic hydrocarbons whereas others, such as 1,2,5,6-dibenzcarbazol, bear a striking resemblance to these. It was therefore decided to modify the structure of active hydrocarbons by replacing one of the ring carbons with a nitrogen atom. The resulting "aza" compounds of benzpyrene and methylcholanthrene not only failed to produce liver tumors but also lost practically all their ability to produce local tumors.

As the ultimate objective of all tests of carcinogenic agents is to throw some light on the mechanism of spontaneous tumor genesis, it would be desirable to learn not only what chemical structures are associated with the ability to induce tumors, but what reactions may take place between the carcinogenic agent and the body tissues. Preliminary studies of the metabolism of carcinogens have indicated that a certain fraction of the injected or ingested hydrocarbon is excreted unchanged, another fraction has not been traced, and a third fraction is excreted in the form of hydroxy, quinone, or other derivatives of the original compound (4, 5, 10, 19).

The chemical modification of hydrocarbons *in vivo* demonstrates that substances present in mammalian tissues can react chemically with carcinogenic hydrocarbons, but since the derivatives thus far identified are relatively inactive their formation might appear to be a process of "detoxification" rather than a part of the chemical pathway responsible for tumor production. The production of neoplasms may depend, of course, upon some direct physical action of the hydrocarbon such as a change in surface forces or tissue permeability, but it might equally well involve a chemical combination, as yet undiscovered, between the carcinogen and substances in the tissue. If the substances resulting from any such interactions were intermediates in the process of carcinogenesis they might themselves be highly carcinogenic.

On this hypothesis a number of compounds were synthesized that contained a hydrocarbon nucleus joined to various radicals theoretically available in tissues. Among the compounds thus tested were hydroxy derivatives and combinations of hydrocarbons with proteins, cysteine, amines and other radicals containing oxygen, nitrogen, sulfur, and halides. None showed sufficient activity to suggest that it might be an intermediate in the process of tumor induction.

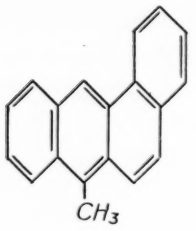
These few remarks serve to indicate some of the lines of thought that influenced the choice of substances to be tested. The detailed reasons for selecting many of them, as well as the chemical implications that may be drawn from the results of the tests, lie for the most part beyond the scope of this paper; our chief purpose is to present factual data on the carcinogenic activity of a number of new hydrocarbon derivatives.

MATERIALS AND METHODS

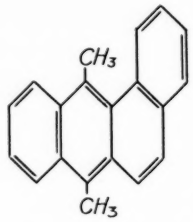
Young male mice of the C3H and Swiss strains were obtained from the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine. They were kept in groups of 5 in metal cages, and fed on Purina dog chow and water with supplements of crude cod liver oil.

These two strains were used since they have a somewhat different incidence of spontaneous tumors. The C3H strain, developed by Strong (23), has been widely used in experimental tumor work. A high percentage of the females develop spontaneous carcinoma of the breast, but tumors of this type practically never occur in the males. In old age both males and females develop occasional pulmonary adenomas, or adenomas of the liver, but spontaneous subcutaneous sarcomas in either sex are rare.

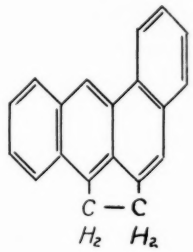
The Swiss strain has not been so widely used as the C3H. Spontaneous adenomas of the lung are frequent in old animals of both sexes, and we have observed occasional adenocarcinomas of the breast in old breeding females. The males fight among themselves, but in spite of frequent and repeated skin wounds in various parts of the body, which often became infected, subcutaneous sarcomas were rarely observed except at the site of injection of a carcinogenic agent. The exceptions were 3 sarcomas in the region of the scrotum found in 1,530 autopsies. Swiss males occasionally develop spontaneous scrotal hernias, which may become secondarily infected. The 3 scrotal



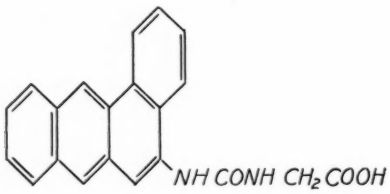
10-Methyl-1,2-benzanthracene



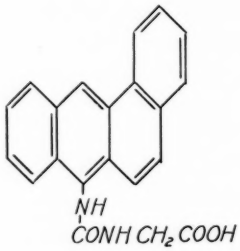
9,10-Dimethyl-1,2-benz-anthracene



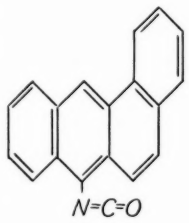
4,10-Ace-1,2-benzanthracene



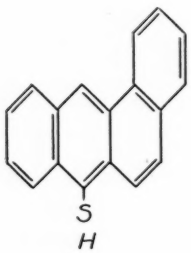
1,2-Benzanthryl-3-carbamido-acetic acid



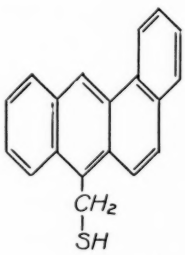
1,2-Benzanthryl-10-carb-amido acetic acid



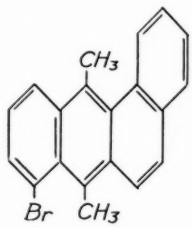
1,2-Benzanthryl-10-iso-cyanate



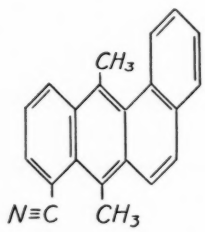
1,2-Benzanthryl-10-mercaptan



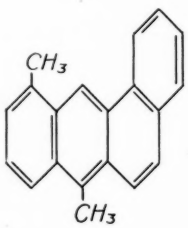
1,2-Benzanthryl-10-methyl-mercaptan



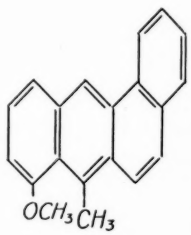
5-Bromo-9,10-dimethyl-1,2-benzanthracene



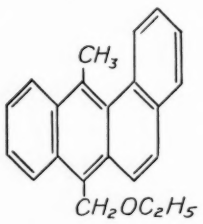
5-Cyano-9,10-dimethyl-1,2-benzanthracene



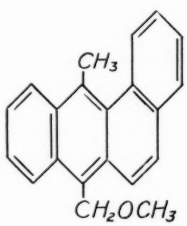
8,10-Dimethyl-1,2-benz-anthracene



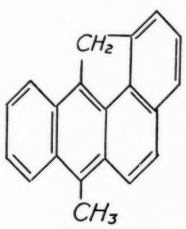
5-Methoxy-10-methyl-1,2-benzanthracene



9-Methyl-10-ethoxymethyl-1,2-benzanthracene



9-Methyl-10-Methoxymethyl-1,2-benzanthracene



10-Methyl-1',9-methylene-1-2-benzanthracene

PLATE I.—Active compounds.

sarcomas were found in association with periorchitis, but a frank hernia was demonstrated in only 1 case.

When the mice were 3 to 5 months old the hydrocarbon to be tested was injected under the skin of the rump. Tricaprylin, kindly prepared by Dr. E. B. Hershberg, was used as a solvent (17) with a few exceptions as noted in the tables. This is a synthetic triglyceride of caprylic acid, and in addition to its excellent solvent properties it has the advantage of being a pure substance of known structure, unlike sesame oil and other liquid vehicles in common use. Some of the compounds that failed to dissolve completely were injected as suspensions in tricaprylin, and a few were suspended in glycerine. The great majority of the compounds were tested at a constant dosage of 2 mgm., per animal, administered in a single injection.

At weekly intervals after injection the mice were inspected for tumors. All were kept alive as long as possible, and at death were autopsied. All tissues suggestive in the gross of neoplasia were examined histologically. The induction time was computed as the number of days between injection and the first appearance of a readily palpable nodule at the injection site—provided that the nodule showed progressive growth and proved to be a malignant tumor on histological examination. Practically all the verified tumors were either fibrosarcomas or rhabdomyosarcomas.

Certain arbitrary standards were adopted as minimal criteria of the adequacy of the tests. No compound was considered inactive unless it had failed to produce tumors after administration to at least 20 mice, of which at least 10 survived for 6 months or more after injection. Tumors appearing elsewhere than at the site of injection are noted in the tables, but were not considered as evidence of carcinogenic activity. Compounds producing malignant tumors at the injection site in one or more of the test mice were arbitrarily classed as "active," even though it is realized that the induction of a single tumor is weak evidence of carcinogenic activity. In this connection it might be mentioned that in another series of experiments involving the subcutaneous injection of India ink, a subcutaneous sarcoma arose in one of 40 C3H mice at the site of injection of the ink. Commercial India ink has been injected into innumerable experimental animals without producing tumors, and we do not consider this one growth sufficient justification for placing it in the increasing list of carcinogenic agents.

The great majority of the compounds tested were substitution products of the four familiar hydrocarbons, 1,2-benzanthracene, 20-methylcholanthrene, 3,4-benzpyrene, and 1,2,5,6-dibenzanthracene. The derivatives of each and an additional group of miscellaneous substances will be considered separately in a series of papers. Part I (12) dealt with chrysene derivatives and the present section, Part II, will be devoted to derivatives of 1,2-benzanthracene.

Carcinogenic Tests On 1,2-Benzanthracene Derivatives

Of the 6 possible hydrocarbons consisting of 4 condensed aromatic rings (3) 1,2-benzanthracene has been the most thoroughly studied from the point of view of carcinogenic derivatives. Although 1,2-benzanthracene itself is inactive (18) some of its methyl and dimethyl substitution products are among the most rapidly acting agents known. About 100 compounds that may be considered immediate derivatives of 1,2-benzanthracene have been synthesized and tested, as outlined in reviews by Fieser (15) and by Cook and his associates (7, 2) and listed in a survey by Hartwell (18), and over a third of them have produced tumors in mice or rats when applied by skin painting or injection. The present paper reports the results of tests on 38 additional derivatives.

In order to provide a basis for comparison control tests were carried out with the 4,10-ace-(or dimethylene), 10-methyl-, and 9,10-dimethyl- derivatives of 1,2-benzanthracene, three compounds that are among the most actively carcinogenic derivatives of 1,2-benzanthracene hitherto reported (20). In our hands they induced tumors in an average time of 161 days, 128 days, and 100 days respectively.

RESULTS

The results obtained with the new derivates of 1,2-benzanthracene are presented in Tables II and III, which are for the most part self-explanatory. Table I gives the details of the tests on the 3 active control substances; Table II includes the 12 compounds that produced tumors; and Table III contains the 26 inactive compounds. Several of the derivatives deserve special comment.

1,2-Benzanthryl-3-Carbamidoacetic Acid
1,2-Benzanthryl-10-Carbamidoacetic Acid

Synthesized by Dr. Hugh J. Creech, these are closely related to the compounds developed by Creech and Franks in an attempt to obtain antigenic carcinogens (8); though theirs showed antigenic properties the preservation of carcinogenic activity was not clearly demonstrated. The new compounds under discussion are both sparingly soluble in weak aqueous solutions of sodium hydroxide, and the only tumors obtained followed the injection of aqueous solutions or suspensions. But since only a single tumor was

produced in each instance, neither of these compounds is sufficiently potent to render it useful as a water-soluble carcinogen. Such a compound is probably available in ε-(1,2,5,6,-dibenzanthryl-9-carbamido)-caproic acid, as will be reported in a later paper (14).

None of the 6 other carbamido-linked substitution products of 1,2-benzanthracene (Table III) produced tumors, a particularly disappointing outcome in the case of the two conjugated proteins prepared by linking horse-serum albumin to benzanthracene. The successful synthesis of these conjugated proteins *in vitro* (9) suggests the theoretical possibility of a protein-hydrocarbon combination *in vivo,* furnishing a hypothetical point of attack by a carcinogenic agent on living tissues. An attempt was made in collaboration with Dr. R. Norman Jones to demonstrate a protein-hydrocarbon complex in extracts of the tissues of rats injected with dibenzanthracene, but serious technical difficulties were encountered and the experiment was not successful.

Seven other sulfur-containing derivatives, including 4 thiocyanates, 1 isothiocyanate and two containing cysteine, were tested with negative results (Table III). The thiocyanate groups were substituted in the benzanthracene molecule at the "active" 9- and 10- positions, and since these positions are optimal for the expression of the carcinogenic effects of other substituents it is doubtful that any monothiocyanate of 1,2-benzanthracene will prove active.

Table I: Active Control Compounds

Compound	Date of injection	Number of mice	Strain	Dose in mgm.	Vehicle*	Route	Effectual total†	Tumors at site of injection	Induction time of earliest tumor, days	Average induction time, days	Transplants	Comments
10-Methyl-1, 2-benzanthracene	Feb. 29, 1940	10	Swiss	5.0	0.2 cc tricap.	subcut.	10	7	96	128	....	2 mice with pulmonary adenoma at 96 and 231 days respectively.
9, 10-Dimethyl-1, 2-benzanthracene	Jan. 9, 1940	20	Swiss	2.0	0.1 cc. tricap.	subcut.	16	10	67	100	....	2 mice with epidermoid carcinoma, 6 with leukemia, and 3 with adenoma of lung, the latter at 100, 112, and 114 days respectively.
	Oct. 28, 1941	15	Swiss	8.0	0.6 cc tricap.	subcut.	5	5	86	101	....	
4, 10-Ace-1, 2-benzanthracene	Oct. 28, 1941	20	C3H	2.0	0.2 cc tricap.	subcut.	18	6	99	161	....	

* tricap = tricaprylin.

† Effectual total = number of mice alive when first tumor appeared.

1,2-Benzanthryl-10-Isocyanate

Isocyanates of 1,2-benzanthracene have not previously been tested for carcinogenic properties. Of the 3 available in this series 1,2-benzanthryl-10-isocyanate gave a single tumor, while the 3-isocyanate and the 10-methyl-3-isocyanate were inactive. Since 10-methyl-1,2-benzanthracene is such a potent carcinogen the weak activity of a compound with isocyanate in the 10- position would suggest that the isocyanate group has limited ability to confer carcinogenic properties, a conclusion that gains support from the negative results obtained with the other 2 isocyanates. However, we have observed (14) that the substitution of isocyanate in the 9- position of dibenzanthracene results in an increase of activity over that of the parent compound, and here again the nature of the substituent group may be of less importance than the molecular position of substitution and the structure of the parent molecule.

1,2-Benzanthryl-10-Mercaptan
1,2-Benzanthryl-10-Methylmercaptan

These sulfur-containing derivatives both proved to be of only weak carcinogenic activity, yet they have considerable theoretical interest. Wood and Fieser (24), in their article describing the syntheses, suggest among other things that sulfur derivatives of carcinogens, formed *in vivo,* may represent biological intermediates in the process of carcinogenesis, or of "detoxification," or both. It will be noted that in one instance carcinogenic activity was conferred on the inert 1,2-benzanthracene molecule by substituting a sulfhydryl group in the 10- position, whereas in the other instance the potent carcinogen, 10-methyl-1,2-benzanthracene, was largely inactivated by substituting sulfhydryl for one of the methyl hydrogens. In these compounds the presence of sulfur in the substituent group appears to have less biological importance than the position of substitution.

5-Bromo-9,10-Dimethyl-1,2-Benzanthracene

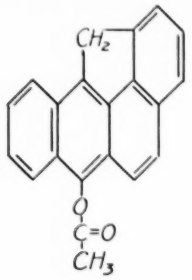
This is the product of substituting bromine in the highly carcinogenic 9,10-dimethyl-1,2-benzanthracene molecule. The tests showed very little loss of activity, and tumors appeared in all surviving mice in an average time of only 117 days. The trimethyl analogue, 5,9,10-trimethyl-1,2-benzanthracene, which Bachmann and his co-workers (1) tested by skin painting, appears to be less active.

TABLE II: ACTIVE COMPOUNDS

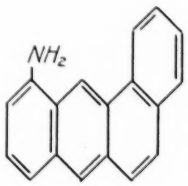
Compound	Date of injection	Number of mice	Strain	Dose in mgm.	Vehicle*	Route	Effectual total†	Tumors at site of injection	Induction time of earliest tumor, days	Average induction time, days	Transplants	Comments
1, 2-Benzanthryl-3-carbamido-acetic acid	Nov. 14, 1939	30	Swiss	3×1.0	0.5 cc H_2O	subcut.	20	1	310	...	yes	2 mice with pulmonary adenoma at 394 and 681 days respectively.
	Mar. 26, 1940	15	Swiss	1.0	0.5 cc H_2O	subcut.	9	0	...	...	...	2 mice with pulmonary adenoma at 310 and 569 days respectively.
	Aug. 12, 1941	15	C3H	2.0	0.2 cc tricap.	subcut.	13	0	...	...	...	
1, 2-Benzanthryl-10-carbamido-acetic acid	Nov. 7, 1939	10	Swiss	4×1.0	0.5 cc H_2O	subcut.	6	1	643	...	...	
	Nov. 14, 1939	15	Swiss	4×1.0	0.5 cc H_2O	subcut.	6	0	...	...	...	1 mouse with pulmonary adenoma at 538 days.
	Mar. 26, 1940	15	Swiss	1.0	0.5 cc H_2O	subcut.	8	0	...	...	...	1 mouse with pulmonary adenoma at 115 days.
	Sept. 9, 1941	10	C3H	2.0	0.2 cc tricap.	subcut.	8	0	...	...	...	
1, 2-Benzanthryl-10-isocyanate	Nov. 14, 1939	10	Swiss	2.0	0.2 cc tricap.	subcut.	6	0	...	...	...	1 mouse with pulmonary adenoma at 622 days.
	"	5	Swiss	4.0	0.3 cc tricap.	subcut.	1	0	...	...	...	1 mouse with epidermoid carcinoma of bladder at 123 days.
	Apr. 22, 1940	10	C3H	1.0	0.2 cc H_2O	subcut.	9	0	...	...	...	
	"	15	Swiss	1.0	0.2 cc H_2O	subcut.	14	1	332	...	...	3 mice with pulmonary adenoma at 451, 628, and 777 days respectively.
1, 2-Benzanthryl-10-mercaptan	Apr. 22, 1940	10	Swiss	4.0	0.2 cc tricap.	subcut.	10	0	...	...	...	1 mouse with pulmonary adenoma at 451 days.
	"	20	Swiss	2.0	0.1 cc tricap.	subcut.	19	0	...	...	...	1 mouse with pulmonary adenoma at 658 days.
	"	10	C3H	2.0	0.1 cc tricap.	subcut.	9	1	281	...	yes	
	Aug. 19, 1941	20	C3H	2.0	0.2 cc tricap.	subcut.	16	2	155	173	...	
1, 2-Benzanthryl-10-methyl-mercaptan	Feb. 29, 1940	15	Swiss	2.0	0.1 cc tricap.	subcut.	10	0	...	...	...	2 mice with pulmonary adenomas at 408 and 441 days respectively.
	Mar. 4, 1941	10	C3H	2.0	0.2 cc tricap.	subcut.	9	1	241	...	...	1 mouse with leukemia.
5-Bromo-9, 10-dimethyl-1, 2-benzanthracene	July 15, 1941	20	C3H	2.0	0.2 cc tricap.	subcut.	19	19	84	117	...	1 mouse with leukemia.
5, cyano-9, 10-dimethyl-1, 2-benzanthracene	Sept. 9, 1941	5	C3H	2.0	0.2 cc tricap.	subcut.	2	2	94	97	...	
8, 10-Dimethyl-1, 2-benzanthracene	Oct. 17, 1939	5	C3H	1.0	0.1 cc tricap.	subcut.	5	5	140	175	...	
	"	5	Swiss	1.0	0.1 cc tricap.	subcut.	3	1	147	...	...	1 mouse with pulmonary adenoma at 172 days.
	"	5	Swiss	2.0	0.2 cc tricap.	subcut.	1	0	...	...	...	1 mouse with pulmonary adenoma at 353 days.
	Aug. 19, 1941	10	C3H	2.0	0.2 cc tricap.	subcut.	9	4	113	133	...	
	"	10	Swiss	2.0	0.2 cc tricap.	subcut.	3	0	...	...	...	
5-Methoxy-10-methyl-1, 2-benzanthracene	Feb. 29, 1940	10	Swiss	2.0	0.2 cc tricap.	subcut.	6	0	...	...	...	1 mouse with pulmonary adenoma at 583 days.
	Jan. 14, 1941	20	C3H	2.0	0.2 cc tricap.	subcut.	15	7	100	198	yes	
9-Methyl-10-ethoxymethyl-1, 2-benzanthracene.	Dec. 10, 1940	20	C3H	2.0	0.2 cc tricap.	subcut.	19	6	176	244	yes	
9-Methyl-10-methoxymethyl-1, 2-benzanthracene	Nov. 12, 1940	20	C3H	2.0	0.2 cc tricap.	subcut.	12	3	238	335	...	
10-Methyl-1'9-methylene-1, 2-benzanthracene	Nov. 7, 1939	15	Swiss	1.0	0.2 cc tricap.	subcut.	2	1	441	...	...	1 mouse with pulmonary adenoma at 519 days.
	"	5	Swiss	2.0	0.3 cc tricap.	subcut.	5	2	231	258	...	1 mouse with lymphoma at 330 days.
	Feb. 25, 1941	20	C3H	2.0	0.2 cc tricap.	subcut.	19	7	149	218	...	

* tricap = tricaprylin.

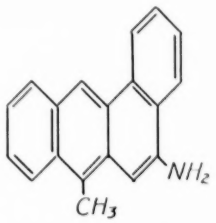
† Effectual total = number of mice alive when first tumor appeared. In groups in which no tumors appeared, the number alive 6 months after injection is used.



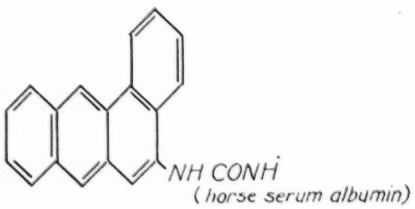
10-Acetoxy-1',9-methylene-1,2-benzanthracene



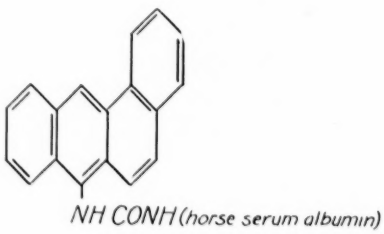
8-Amino-1,2-benzanthracene



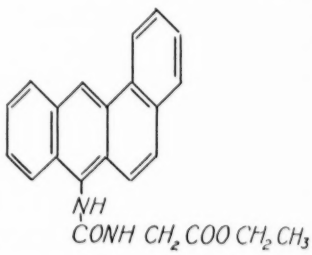
3-Amino-10-methyl-1,2-benzanthracene



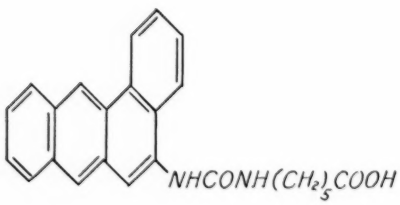
1,2-Benzanthryl-3-carbamido-horse serum albumin



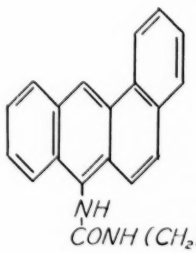
1,2-Benzanthryl-10-carbamido-horse serum albumin



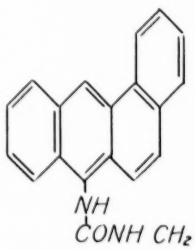
Ethyl ester of 1,2-benzanthryl-10-carbamidoacetic acid



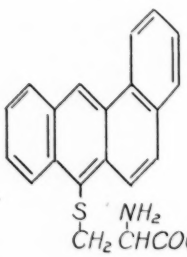
ε-(1,2-Benzanthryl-3-carbamido)-caproic acid



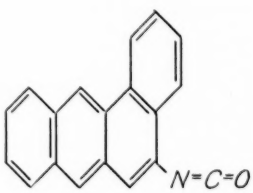
ε-(1,2-Benzanthryl-10-carbamido)-caproic acid



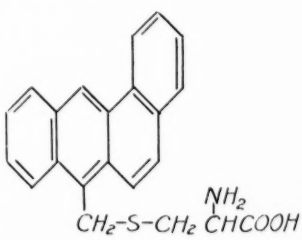
1,2-Benzanthryl-10-carbamido-ethanol



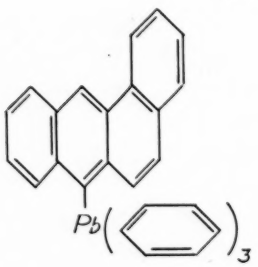
1,2-Benzanthryl-10-S-dl-cysteine



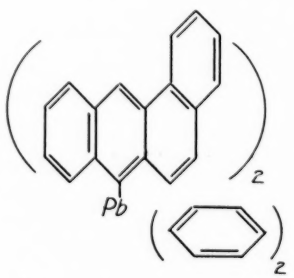
1,2-Benzanthryl-3-isocyanate



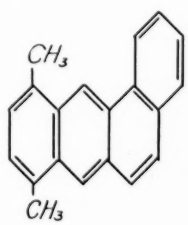
1,2-Benzanthryl-10-methyl-S-l-cysteine



10-(1,2-Benzanthryl)-triphenyllead

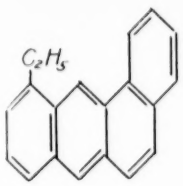


10-(Di-1,2-benzanthryl)-diphenyllead

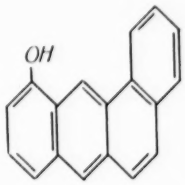


5,8-Dimethyl-1,2-benzanthracene

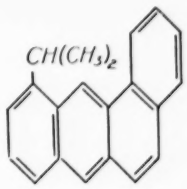
PLATE II.—Inactive compounds.



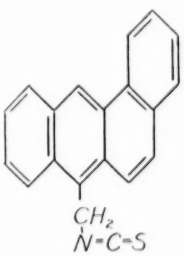
8-Ethyl-1,2-benzanthracene



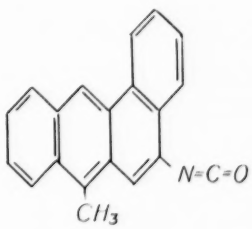
8-Hydroxy-1,2-benzanthracene



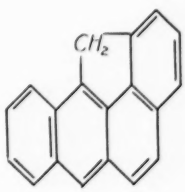
8-Isopropyl-1,2-benzanthracene



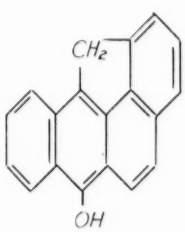
10-Isothiocyanomethyl-1,2-benzanthracene



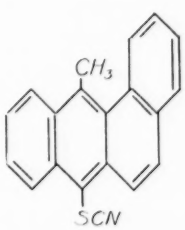
10-Methyl-1,2-benzanthryl-3-isocyanate



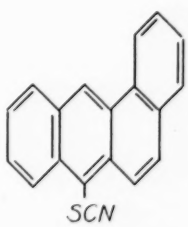
1',9-Methylene-1,2-benzanthracene



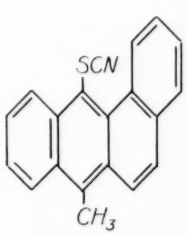
1',9-Methylene-1,2-benz-10-anthranol



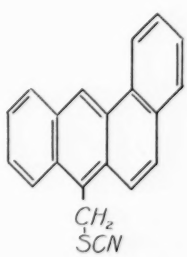
9-Methyl-10-thiocyano-1,2-benzanthracene



10-Thiocyano-1,2-benzanthracene



9-Thiocyano-10-methyl-1,2-benzanthracene



10-Thiocyanomethyl-1,2-benzanthracene

PLATE III.—Inactive compounds (continued).

TABLE III: INACTIVE COMPOUNDS

Compound	Date of injection	Number of mice	Strain	Dose in mgm.	Vehicle*	Route	Number of mice alive at 6 months	Comments
10-Acetoxy-1'9-methylene-1, 2-benzanthracene	Jan. 25, 1940	20	Swiss	1.5	0.2 cc. tricap.	subcut.	18	1 mouse with pulmonary adenoma at 530 days;
	Aug. 12, 1941	15	C3H	2.0	0.2 cc. tricap.	subcut.	11	1 with sarcoma of shoulder at 496 days, not at site of injection.
8-Amino-1, 2-benzanthracene	Oct. 17, 1939	5	C3H	1.0	1.0 cc. tricap.	subcut.	3	1 mouse with pulmonary adenoma at 345 days.
	"	5	Swiss	1.0	1.0 cc. tricap.	subcut.	5	
	"	5	Swiss	2.0	0.2 cc. tricap.	subcut.	1	
3-Amino-10-methyl-1, 2-benzanthracene	Dec. 17, 1940	20	C3H	2.0	0.2 cc. tricap.	subcut.	11	
1, 2-Benzanthryl-3-carbamido-horse serum albumin	July 10, 1940	15	C3H	2.0	1.0 cc. water	subcut.	10	
	"	15	Swiss	2.0	1.0 cc. water	subcut.	10	
1, 2-Benzanthryl-10-carbamido-horse serum albumin	July 10, 1940	15	C3H	2.0	0.7 cc. water	subcut.	9	2 mice with pulmonary adenoma at 353 and 497 days respectively.
	"	15	Swiss	2.0	0.7 cc. water	subcut.	7	1 mouse developed sarcoma of foot.
Ethyl ester of 1, 2-benzanthryl-10-carbamidoacetic acid	Nov. 14, 1939	20	Swiss	2.0	0.2 cc. tricap.	subcut.	14	
	Sept. 9, 1941	10	C3H	2.0	0.2 cc. tricap.	subcut.	6	
ϵ-(1, 2 Benzanthryl-3-carbamido)-caproic acid	Nov. 21, 1939	25	Swiss	3×0.5	0.5 cc. water	subcut.	5	1 mouse with pulmonary adenoma at 253 days.
	Dec. 12, 1939	10	Swiss	1.0	1.0 cc. water	intra-peritoneal	4	
	Mar. 11, 1941	10	C3H	2.0	0.2 cc. tricap.	subcut.	9	
ϵ-(1, 2-benzanthryl-10-carbamido)-caproic acid	Nov. 21, 1939	25	Swiss	3×0.5	0.5 cc. water	subcut.	6	1 mouse with pulmonary adenoma at 811 days.
	Dec. 12, 1939	15	Swiss	1.0	1.0 cc. water	intra-peritoneal	7	1 mouse with pulmonary adenoma at 253 days.
	Mar. 11, 1941	15	C3H	2.0	0.2 cc. tricap.	subcut.	14	
1, 2-Benzanthryl-10-carbamidoethanol	Nov. 21, 1939	25	Swiss	1.0	0.25 cc. tricap.	subcut.	9	1 mouse with pulmonary adenoma at 584 days.
	Mar. 4, 1941	10	C3H	2.0	0.2 cc. tricap.	subcut.	9	
1, 2-Benzanthryl-10-S-d1-cysteine	Dec. 10, 1940	20	C3H	2.0	0.2 cc. tricap.	subcut.	11	
1, 2-Benzanthryl-3-isocyanate	Nov. 14, 1939	10	Swiss	2.0	0.2 cc. tricap.	subcut.	7	
	Jan. 14, 1939	5	Swiss	4.0	0.4 cc. tricap.	subcut.	5	1 mouse with pulmonary adenoma at 415 days.
	Apr. 22, 1940	10	C3H	1.0	0.2 cc. water	subcut.	9	
	"	15	Swiss	1.0	0.2 cc. water	subcut.	14	1 mouse with pulmonary adenoma at 371 days.
1, 2-Benzanthryl-10-methyl-S-1-cysteine	Jan. 25, 1940	15	Swiss	2.0	0.2 cc. glycerine	subcut.	7	
	Feb. 25, 1941	10	C3H	2.0	0.2 cc. tricap.	subcut.	7	
10-(1, 2-Benzanthryl)-triphenyllead	June 10, 1941	20	C3H	2.0	0.2 cc. tricap. (suspension)	subcut.	10	
10-(Di-1, 2-benzanthryl)-diphenyllead	June 10, 1941	20	C3H	2.0	0.2 cc. tricap. (suspension)	subcut.	12	

* tricap = tricaprylin.

TABLE III: INACTIVE COMPOUNDS—*Continued*

Compound	Date of injection	Number of mice	Strain	Dose in mgm.	Vehicle*	Route	Number of mice alive at 6 months	Comments
5, 8-Dimethyl-1, 2-benzanthracene	Aug. 29, 1939	15	C3H	1.0	0.7 cc. tricap.	subcut.	14	
	"	10	Swiss	1.0	0.7 cc. tricap.	subcut.	10	2 mice with pulmonary adenoma at 481 and 530 days respectively and 1 with uterine leiomyoma at 551 days.
	Sept. 16, 1939	5	C3H	2.0	0.1 cc. tricap.	subcut.	4	
	"	10	C3H	2.0	0.25 cc. glycerine	subcut.	9	
	"	5	Swiss	2.0	0.1 cc. tricap.	subcut.	5	
	"	10	Swiss	2.0	0.25 cc. glycerine	subcut.	10	1 mouse with pulmonary adenoma at 471 days.
8-Ethyl-1, 2-benzanthracene	Oct. 10, 1939	10	C3H	2.0	0.05 cc. tricap.	subcut.	9	
	"	5	Swiss	2.0	0.05 cc. tricap.	subcut.	1	
	"	5	C3H	1.0	0.2 cc. glycerine	subcut.	4	
	"	10	C3H	1.0	0.2 cc. glycerine	subcut.	5	3 mice with pulmonary adenoma at 430, 569, and 594 days respectively.
8-Hydroxy-1, 2-benzanthracene	Oct. 10, 1939	5	C3H	2.0	0.1 cc. tricap.	subcut.	0	
	"	5	Swiss	2.0	0.1 cc. tricap.	subcut.	4	
	Jan. 7, 1941	14	C3H	2.0	0.2 cc. tricap.	subcut.	12	
8-Isopropyl-1, 2-benzanthracene	Feb. 10, 1940	20	C3H	2.0	0.2 cc. tricap.	subcut.	13	
10-Isothiocyanomethyl-1, 2-benzanthracene	May 19, 1941	20	C3H	2.0	0.2 cc. tricap.	subcut.	16	
10-Methyl-1, 2-benzanthryl-3-isocyanate	Dec. 17, 1940	20	C3H	2.0	0.2 cc. tricap.	subcut.	14	
1′, 9-Methylene-1, 2-benzanthracene	Aug. 29, 1939	15	C3H	1.0	0.5 cc. tricap.	subcut.	14	1 mouse with 3 tumors: pulmonary adenoma, hepatic adenoma, and benign hemangioma of rump at 539 days.
	"	15	Swiss	1.0	0.5 cc. tricap.	subcut.	10	
	Sept. 16, 1939	5	C3H	2.0	0.1 cc. tricap.	subcut.	5	
	"	5	Swiss	2.0	0.1 cc. tricap.	subcut.	2	
	"	10	C3H	2.0	0.25 cc. glycerine	subcut.	7	
	"	5	Swiss	2.0	0.25 cc. glycerine	subcut.	1	
1′, 9-Methylene-1, 2-benz-10-anthranol	Jan. 9, 1940	10	Swiss	1.0	0.03 cc. tricap.	subcut.	3	1 mouse with pulmonary adenoma at 608 days.
	"	5	Swiss	4.0	0.12 cc. tricap.	subcut.	5	
	June 24, 1941	15	C3H	2.0	0.2 cc. tricap.	subcut.	10	
9-Methyl-10-thiocyano-1, 2-benzanthracene	Dec. 17, 1940	20	C3H	2.0	0.2 cc. tricap.	subcut.	17	
	June 10, 1941	20	C3H	2.0	0.2 cc. tricap.	subcut.	16	
10-Thiocyano-1, 2-benzanthracene	May 6, 1941	20	C3H	2.0	0.2 cc. tricap.	subcut.	14	
9-Thiocyano-10-methyl-1, 2-benzanthracene	June 3, 1941	15	C3H	2.0	0.2 cc. tricap.	subcut.	15	
10-Thiocyanomethyl-1, 2-benzanthracene	May 13, 1941	20	C3H	2.0	0.2 cc. tricap.	subcut.	13	

* tricap = tricaprylin.

The presence of bromine in the molecule opens the possibility of substituting radioactive bromine to serve as a tracer in studying the metabolism of the carcinogen at the site of tumor induction, and a similar suggestion has previously been made concerning the sulfur atom in 4,9-dimethyl-5,6-benzthiophanthrene (11). However, work on the latter compound at Dr. Fieser's laboratory has not yet perfected a synthesis sufficiently economical of sulfur to be practicable, and the present synthesis of the 5-bromo compound is likewise not adapted to the introduction of radioactive bromine.

5-Cyano-9,10-Dimethyl-1,2-Benzanthracene

Only a few milligrams of this material were available for testing, but the meager data suggest that it is highly active. Shear (21) found comparable activity in the closely related compound, 5-cyano-10-methyl-1,2-benzanthracene, whereas his 6-cyano-isomer was inactive.

8,10-Dimethyl-1,2-Benzanthracene

Fourteen of the 28 possible dimethyl isomers of 1,2-benzanthracene had previously been tested (18). This new member of the series, only moderately active, serves again to indicate the importance of a substituent at the 9- or 10- positions in imparting activity to benzanthracene derivatives. In our hands the 5,8-dimethyl isomer yielded no tumors, nor did the 8-amino, 8-ethyl, 8-isopropyl or 8-hydroxy derivatives, and Shear (22) found 8-methyl-1,2-benzanthracene inactive. The evidence at hand indicates that benzanthracene derivatives with substituents at the 8 position are likely to be carcinogenically weak or inert.

5-Methoxy-10-Methyl-1,2-Benzanthracene
9-Methyl-10-Ethoxymethyl-1,2-Benzanthracene
9-Methyl-10-Methoxymethyl-1,2-Benzanthracene

These 3 compounds have in common the presence of oxygen in one of the substituent groups. Similar compounds in the past have shown at best only slight or moderate activity (15). If the parent substances be considered as 9-methyl- and 10-methyl-1,2-benzanthracene the results indicate that the substitution of the oxygen-containing functional groups resulted in each case in a partial loss of activity.

10-Methyl-1′,9-Methylene-1,2-Benzanthracene

This compound, as previously noted, is related structurally to both 1,2-benzanthracene and benzpyrene. The 1′,9-methylene group completes a 5-carbon ring structure in the position occupied by a 6-carbon ring in benzpyrene. However, the 5-membered ring in the 1′,9- position does not appear to confer any carcinogenic properties, since the compound proved weaker than its parent substance, 10-methyl-1,2-benzanthracene. It should also be noted (Table III) that 1′,9-methylene-1,2-benzanthracene, 1′,9-methylene-1,2-benz-10-anthranol, and 10-acetoxy-1′,9-methylene-1,2-benzanthracene were completely inactive. The results obtained with these compounds do not accord with the suggestion of Bergman (6) that substituents "produce active carcinogens if they imitate rings which enhance tumor production."

Amino Compounds

8-amino- and 3-amino-10-methyl-1,2-benzanthracene failed to produce tumors. The 8- and 3- positions may both be considered unfavorable for testing the effect of amine as an activating substituent in benzanthracene, for the amino substituent is not incompatible with carcinogenic activity, as is shown by the fact that Shear (21) obtained tumors with 10-amino-1,2-benzanthracene; and we have found 9-amino-1,2,5,6-dibenzanthracene to be very active (14).

SUMMARY

1. Thirty-eight derivatives of 1,2-benzanthracene have been tested on mice for carcinogenic activity.

2. Twelve of these compounds produced one or more tumors each, whereas 26 were inactive.

3. Substitution of functional groups in the benzanthracene nucleus resulted in the formation of weak or inactive compounds, in keeping with the results of other workers. Exceptions to this rule were found in the cases of 5-bromo- and 5-cyano-9,10-dimethyl-1,2-benzanthracene, both of which proved to be very active.

4. The substitution of bromine for the methyl group in the 5- position of 5,9,10-trimethyl-1,2-benzanthracene apparently enhanced activity.

5. Four thiocyano and 2 amino substitution products were inactive.

6. The substitution of a methylene group in the 1′,9- position of benzanthracene results in a ring structure with features common to benzpyrene and benzanthracene. However, compounds with this structural feature had little or no activity. In one instance the activity of a potent compound, 10-methyl-1,2-benzanthracene, was greatly diminished by introducing a 1′,9-methylene substituent.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the skillful help of Miss Eleanor Beaulac, who carried out many of the injections and prepared the tissue sections; and of Mrs. Nancy Meegan, who cared for the animals and recorded the first appearance of many of the tumors.

REFERENCES

1. Bachmann, W. E., Kennaway, E. L., and Kennaway, N. M. The Rapid Production of Tumours by Two New Hydrocarbons. Yale J. Biol. & Med., **11**:97-102. 1938.
2. Badger, G. M., Cook, J. W., Hewett, C. L., Kennaway, E. L., Kennaway, N. M., Martin, R. H., and Robinson, A. M. The Production of Cancer by Pure Hydrocarbons. V. Proc. Roy. Soc., London, s. B, **129**:439-467. 1940.
3. Barry, G., Cook, J. W., Haslewood, G. A. D., Hewett, C. L., Hieger, I., and Kennaway, E. L. The Production of Cancer by Pure Hydrocarbons. III. Proc. Roy. Soc., London, s. B, **117**:318-351. 1935.
4. Berenblum, I., Crowfoot, D., Holiday, E. R., and Schoental, R. The Metabolism of 3,4-Benzpyrene in Mice and Rats. II. The Identification of the Isolated Products as 8-Hydroxy-3,4-Benzpyrene and 3,4-Benzpyrene-5,8-Quinone. Cancer Research, **3**:151-158. 1943.
5. Berenblum, I., and Schoental, R. The Metabolism of 3,4-Benzpyrene in Mice and Rats. I. The Isolation of a Hydroxy and a Quinone Derivative, and a Consideration of Their Biological Significance. Cancer Research, **3**:145-150. 1943.
6. Bergman, F. On the Mechanism of Tumor Production by Chemical Agents. Cancer Research, **2**:660-663. 1942.
7. Cook, J. W. Polycyclic Aromatic Compounds. Annual Reports on the Progress of Chemistry for 1942. Issued by the Chemical Society, **39**:155-191. 1943.
8. Creech, H. J., and Franks, W. R. Compounds Synthesized from Proteins and Carcinogenic Hydrocarbons. Am. J. Cancer, **30**:555-562. 1937.
9. Creech, H. J., and Jones, R. N. The Conjugation of Horse Serum Albumin with 1,2-Benzanthryl Isocyanates. J. Am. Chem. Soc., **62**:1970-1975. 1940.
10. Dobriner, K., Rhoads, C. P., and Lavin, G. I. The Spectroscopic Study of Biological Extracts. II. The Detection, Isolation, and Biological Effects of the Metabolites of 1,2,5,6-Dibenzanthracene. Cancer Research, **2**:95-107. 1942.
11. Dunlap, C. E., and Warren, S. Chemical Configuration and Carcinogenesis. Cancer Research, **1**:953-954. 1941.
12. Dunlap, C. E., and Warren, S. The Carcinogenic Activity of Some New Derivatives of Aromatic Hydrocarbons. I. Compounds Related to Chrysene. Cancer Research, **3**:606-607. 1943.
13. Dunlap, C. E., and Warren, S. The Carcinogenic Activity of Some New Derivatives of Aromatic Hydrocarbons. III. Compounds Related to 3,4-Benzpyrene. (To be published).
14. Dunlap, C. E., and Warren, S. The Carcinogenic Activity of Some New Derivatives of Aromatic Hydrocarbons. IV. Compounds Related to 1,2,5,6-Dibenzanthracene. (To be published).
15. Fieser, L. F. Carcinogenic Activity, Structure, and Chemical Reactivity of Polynuclear Aromatic Hydrocarbons. Am. J. Cancer, **34**:37-124. 1938.
16. Fieser, L. F. Production of Cancer by Polynuclear Hydrocarbons. *In* Cause and Growth of Cancer. Univ. Pennsylvania Bicentennial Conference. Philadelphia: Univ. of Pennsylvania Press. 1940.
17. Hartwell, J. L. The Preparation of Tricaprylin. Am. J. Path., **16**:313-316. 1940.
18. Hartwell, J. L. Survey of Compounds Which Have Been Tested for Carcinogenic Activity. National Cancer Institute, National Institute of Health, United States Public Health Service. 1941.
19. Jones, R. N., Dunlap, C. E., and Gogek, C. J. The Spectrographic Analysis of Carcinogenic Hydrocarbons and Metabolites. IV. The Elimination of 1,2,5,6-Dibenzanthracene from the Rat. Cancer Research, **4**:209-217. 1944.
20. Shear, M. J. Studies in Carcinogenesis. V. Methyl Derivatives of 1:2-Benzanthracene. Am. J. Cancer, **33**:499-537. 1938.
21. Shear, M. J., and Leiter, J. Studies in Carcinogenesis. XIV. 3-Substituted and 10-Substituted Derivatives of 1,2-Benzanthracene. J. Nat. Cancer Inst., **1**:303-336. 1940.
22. Shear, M. J., and Leiter, J. Studies in Carcinogenesis. XVI. Production of Subcutaneous Tumors in Mice by Miscellaneous Polycyclic Compounds. J. Nat. Cancer Inst., **2**:241-258. 1941.
23. Strong, L. C. The Origin of Some Inbred Mice. Cancer Research, **2**:531-539. 1942.
24. Wood, J. L., and Fieser, L. F. Sulfhydryl and Cysteine Derivatives of 1,2-Benzanthracene, 10-Methyl-1,2-Benzanthracene and 3,4-Benzpyrene. J. Am. Chem. Soc., **62**: 2674-2681. 1940.

The Effect of Diets Containing an Abundance of Milk, Liver, Riboflavin, and Xanthine on Methylcholanthrene Carcinogenesis*

L. C. Strong, Ph.D., and Frank H. J. Figge, Ph.D.**

(From the Department of Anatomy, Yale University School of Medicine, New Haven 11, Connecticut)

(Received for publication April 25, 1946)

The numerous attempts to influence the development and growth of neoplasms by means of vitamins and other nutritional elements have been comprehensively summarized by other investigators (8, 9, 20). The experiment described here was stimulated by the observation that the dialyzed ground livers of cancer-resistant mice (JK), exhibit a higher level of xanthine dehydrogenase activity than do the dialyzed liver preparations of mice of a cancer-susceptible (C3H) strain (11). The mice of the JK strain were found also to be more tolerant to salicylaldehyde than were those of the C3H strain (21, 22). Xanthine dehydrogenase is a flavoprotein (2, 13), capable of oxidizing aldehydes as well as xanthines and found in high concentrations in milk and liver (2, 10, 12, 13, 19).

Axelrod and Elvehjem (1) showed that the xanthine dehydrogenase activity of rat liver is greatly reduced in riboflavin deficiency and that this decrease parallels the degree of the deficiency. The effect of feeding excessive amounts of the precursors of xanthine dehydrogenase on enzyme activity of the liver has not been determined.

This paper will be limited to a presentation and discussion of the results of feeding relatively enormous amounts of the dietary precursors of xanthine dehydrogenase to mice of the C3H strain. These mice have a relatively high susceptibility to spontaneous mammary carcinoma and methylcholanthrene tumors (7); and their livers, as compared with those of the resistant JK mice, exhibit a lower xanthine dehydrogenase activity (11). Xanthine, which is one of the normal substrates for xanthine dehydrogenase, was also included in this investigation because excessive amounts of either the substrate or uric acid, its oxidation product, inhibit the activity of xanthine dehydrogenase (10). It was thought that the inclusion of this substance in the diet might reduce the xanthine dehydrogenase activity of the liver, thus creating a physiological state similar to that induced by a deficiency of either riboflavin or protein, precursors of xanthine dehydrogenase. The purpose of these experiments was to ascertain whether the incidence or latent period of methylcholanthrene tumors could be altered by such dietary procedures.

METHODS AND MATERIALS

The basic experimental diet used contained the following ingredients: (a) 20 pounds of freshly ground pig liver; (b) 8 quarts of raw (unpasteurized) milk; (c) 50 pounds of Nurishmix;[1] and (d) 5 pounds Klim brand dried whole milk. These ingredients were thoroughly mixed and kneaded together, then dried and stored in an open container until fed to the mice. This diet will be referred to in this paper as the "Liver, Milk, Nurishmix," or L.M.N. diet.

Liver, in addition to other vitamins of the B complex, contains 10 to 30 mgm. per cent riboflavin (19), or about 10 to 30 times the amount found in muscle. The dried milk contains relatively high concentrations of casein and riboflavin. Raw milk contains free riboflavin and casein, and in addition an abundance of xanthine dehydrogenase (2, 13). Nurishmix contains dried buttermilk and meat scraps, and therefore appears to provide adequate protein and riboflavin even without the added liver and milk. Thus the L.M.N. diet was unusually high in protein (casein) and riboflavin. Some of the mice fed this mixture were given an additional quantity of riboflavin in milk substituted for drinking water. Xanthine was dissolved in the raw milk administered to one group of 11 animals.

Fifty-seven mice of the C3H strain were placed on the L.M.N. diet; 55 of the same strain and age (46 days) were placed on a diet of Nurishmix alone and used as controls. When both groups were 60 days of

* This experiment has been made possible by grants from The Anna Fuller Fund and The Jane Coffin Childs Memorial Fund for Medical Research.

** Rockefeller Fellow on leave from University of Maryland Medical School, 1940-41.

[1] According to the manufacturers (Pratt Food Co.), Nurishmix contains dried buttermilk; beef scraps; wheat germ meal; rolled oats; molasses; iodized salt, 1%; and U.S.P. cod liver oil.

age they were injected subcutaneously on the right side with 1 mgm. of methylcholanthrene dissolved in 0.1 cc. of sesame oil. Another 45 normal C3H mice were kept as a second group of controls in order to ascertain the normal growth rate of nontreated mice on the Nurishmix diet.

Three weeks after the injections of methylcholanthrene, the 57 experimental mice were divided into two main groups, as follows: I. Those continued throughout the experiment on L.M.N. diet—30 mice; and II. Those given fresh raw milk daily, *ad libitum,* in place of water—27 mice. This second group was further subdivided into 3 groups, as indicated in Table I. All the mice that were given raw milk daily drank more liquid than those given water. The average milk intake per mouse per day was 3.5 cc., representing an intake of 0.35 mgm. of riboflavin per mouse in the cases where this was added; this is a huge dose for a mouse, and is approximately equivalent to 15 gm. of riboflavin per day for a 75 kgm. man. When mice on such a regime were examined at autopsy under near-ultraviolet light, the entire intestinal tract exhibited a brilliant yellow fluorescence from the high concentration of riboflavin.

Biweekly determinations of body weight and examinations for nodular masses at the site of injection were made. When a growing tumor became obvious, the body weights of these mice were compared with the body weights of those in the same groups still free of induced tumors. Growth rate of the tumors and survival time of the mice were determined and compared to similar data for the normal controls.

TABLE I: SURVIVAL TIME WITH TUMORS

Data on (a) group of mice used; (b) diet for several groups; (c) No. of mice in each group and average survival time for various groups following appearance of induced fibrosarcomas.

Group	Diet	No. of mice	Survival time, days
A. Control (injected MCA)	Nurishmix + water	55	36.0
A. Normal (non injected)	Nurishmix + water	45	
B. Experimental (injected MCA)	L. M. N. diet	57	27.5
I. L. M. N. diet alone and water		30	27.0
II. L. M. N. diet + raw milk		27	28.0
(a) Raw milk alone		8	29.7
(b) Raw milk + riboflavin*		8	27.7
(c) Raw milk, plus xanthine†, plus riboflavin		11	27.0

*10 mgm. per 100 cc.
†3.3 mgm. per 100 cc.

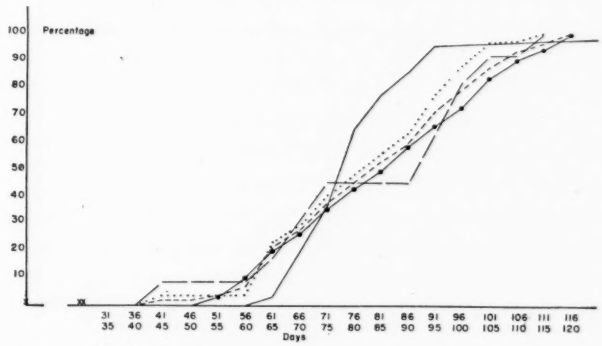


FIG. 1.—Average latent periods. The data are given cumulatively. Percentage of tumors on vertical line; average latent period on base line; data for controls on solid line; for all experimental mice on L.M.N. diet on short dash line; for those experimental mice not receiving a supplement of raw milk (L.M.N. diet alone) on solid dot and long dash line; for experimental mice receiving a supplement of fresh raw milk on dotted line; and for those receiving xanthine and riboflavin added to supplement of fresh raw milk on long dash line. x indicates injection of methylcholanthrene; xx, raw milk riboflavin supplement started.

RESULTS

The mice in the various groups exhibited uniform growth rates. The average latent periods for the various groups are given in Fig. 1. In this graph the data are given cumulatively; that is, the data at any given age period included all mice that had developed actively growing tumors up to that point. The data for the controls (on Nurishmix diet) are given on the solid line; the average data for all the experimental mice on L.M.N. diet (57 mice) are given on the short dash line; the data for those experimental mice not receiving a supplement of raw milk (L.M.N. diet alone) are given on the solid dot and long dash line; the data for those experimental mice (L.M.N. diet) receiving a supplement of fresh raw milk are given on the dotted line; and finally, the data for those mice receiving xanthine and riboflavin added to their supplement of fresh raw milk are given on the long dash line. It will be seen that all the curves for the experimental mice tend to group together and all deviate but slightly from the curve obtained for the control mice kept on Nurishmix diet alone.

Seven mice out of a total of 57 on the L.M.N. diet developed progressively growing tumors before any of

the 55 control mice did. That is, the L.M.N. diet appeared at first to cause an earlier incidence of induced tumors. At 86 to 90 days following the injection of methylcholanthrene, 35 of the 57 mice on L.M.N. diet had developed tumors (60.4 per cent), whereas 46 of the 55 control mice had given rise to tumors (83.3 per cent) in the same time. Thus during the later stages of the experiment the L.M.N. diet appeared to delay the induction of tumors by methylcholanthrene. When a supplement of fresh raw (unpasteurized) milk was given in place of the water that the controls received, there was a closer approach to the situation in respect to induced tumors than was manifested by the controls. On the other hand, when xanthine plus riboflavin was added to the raw milk, a greater deviation from the controls may have been observed. However, this should be verified upon larger groups of mice. It must be admitted that the very high levels of riboflavin and casein exerted little or no protective action against the tumors induced with the 1 mgm. dose of methylcholanthrene. The survival times of the mice after the actively growing tumors were recorded are given in Table I.

DISCUSSION

The 1 mgm. dose of methylcholanthrene injected subcutaneously is relatively high, and may have been so large as completely to overshadow any possible dietary influence. However, a number of other investigators have fed liver in attempts to influence tar, methylcholanthrene, or benzpyrene carcinogenesis with similar results. Watson (25) found that tar cancer in mice was slightly accelerated by feeding liver, and Bonser and Wainman (5, 6) that feeding fresh liver to benzpyrene-painted mice caused a slight acceleration of papilloma formation, but a delay in the development of malignant tumors. Although their experiment involved painting with a less potent carcinogen than methylcholanthrene, their results were in agreement with those reported here. Baumann and Rusch (3, 4) have shown, also, that feeding liver has little or no influence on carcinogenesis induced by ultraviolet light or by the local application of purified hydrocarbons. The possibility of demonstrating an influence of liver, milk, or riboflavin feeding by repeating these experiments with lower doses of methylcholanthrene therefore seems remote.

The investigators who produced hepatomas in rats by feeding *p*-dimethylaminoazobenzene (15, 18) were able to prevent this type of cancer by adding large supplements of liver (5 per cent) or yeast (15 per cent) to the basic rice diet. A year or two later Mori and Nakahara (17) found that whereas feeding liver prevented *p*-dimethylaminoazobenzene hepatomas, it did not inhibit methylcholanthrene or benzpyrene tumors. Sugiura and Rhoads (23) began an investigation to ascertain the nature of the substances in the rice bran extracts, yeast, or beef liver that were responsible for the prevention of *p*-dimethylaminoazobenzene hepatomas. They found that casein alone or riboflavin alone exerted no protective action, but that partial protection was afforded by a supplement of a small amount of riboflavin fed with casein (14). Miller and others (16) studied this same problem, employing diets in which the adequacy of vitamins and proteins was more easily controlled. They concluded that nutritionally adequate diets offered at least partial protection against hepatoma formation, and stated the now generally accepted idea that protective supplements are usually rich in both protein and vitamin B complex, particularly riboflavin, and that nonprotective diets are deficient in at least one of these factors. According to the work of Axelrod and Elvehjem (1), mentioned earlier, a deficiency of either protein or riboflavin would result in a lowered xanthine (oxidase) dehydrogenase activity of the liver.

Thus it appears that *p*-dimethylaminoazobenzene induces hepatomas only in livers with low xanthine dehydrogenase resulting from a deficient or near-deficient diet, for when adequate or excess amounts of liver, yeast, or milk (24), xanthine dehydrogenase precursors, are fed along with *p*-dimethylaminoazobenzene, its carcinogenic action is diminished or noneffective. Carcinogenesis by substances like methylcholanthrene, on the other hand, is not dependent on a deficiency state, and little or no protection is afforded by a diet containing adequate or excess amounts of xanthine dehydrogenase precursors (high casein riboflavin) in the form of liver, milk, and riboflavin supplements.

SUMMARY

A diet of liver supplemented by combinations of raw, unpasteurized milk, riboflavin, and xanthine had little or no influence on the latent period or growth rate of tumors induced in C3H mice by the subcutaneous injection of 1 mgm. doses of methylcholanthrene. In general, the diet supplements stimulated tumors at first and later seemed to have a slight inhibitory effect. This effect was most pronounced in the group of mice receiving raw milk and riboflavin in addition to the basic dried liver, milk, Nurishmix diet. In any case, the effect of diet was so slight that its significance was questionable. This is in contrast to the remarkable inhibition of the carcinogenic action of *p*-dimethylaminoazobenzene observed by other investigators when adequate amounts of yeast, liver, or milk are added to the diet.

REFERENCES

1. Axelrod, A. E., and Elvehjem, C. A. The Xanthine Oxidase Content of Rat Liver in Riboflavin Deficiency. J. Biol. Chem., **140**:725-738. 1941.
2. Ball, E. G. Xanthine Oxidase: Purification and Properties. J. Biol. Chem., **128**:51-67. 1939.
3. Baumann, C. A., and Rusch, H. P. Effect of Diet on Tumors by Ultraviolet Light. Am. J. Cancer, **35**:213-221. 1939.
4. Baumann, C. A., Jacobi, H. P., and Rusch, H. P. The Effect of Diet on Experimental Tumor Production. Am. J. Hyg., **30**:1-6. 1939.
5. Bonser, G. M. Yorkshire Council of the British Empire Cancer Campaign. Ann. Rep., 1940-41. p. 6.
6. Bonser, G. M., and Wainman, L. M. Effect of a Diet Supplemented by Fresh Liver on Induced Skin Tumours in Inbred Mice. J. Path. & Bact., **50**:548-550. 1940.
7. Burdette, W. J., and Strong, L. C. The Inheritance of Susceptibility to Tumors Induced in Mice. I. Tumors Induced by Methylcholanthrene in Five Inbred Strains of Mice. Cancer Research, 3:13-20. 1943.
8. Burk, D., and Winzler, R. J. The Biochemistry of Malignant Tissue. Ann. Rev. Biochem., **13**:487-532. 1944.
9. Burk, D., and Winzler, R. J. Vitamins and Hormones. Vol. II. p. 305-352. Academic Press, Inc., N. Y., 1944.
10. Dixon, M., and Keilin, D. The Action of Cyanide and other Respiratory Inhibitors on Xanthine Oxidase. Proc. Roy. Soc. London, s.B, **119**:159-190. 1936.
11. Figge, F. H. J., and Strong, L. C. Xanthine Oxidase (Dehydrogenase) Activity in Livers of Mice of Cancer-Susceptible and Cancer-Resistant Strains. Cancer Research, **1**:779-784. 1941.
12. Green, D. E. Studies on Reversible Dehydrogenase Systems. II. The Reversibility of the Xanthine Oxidase System. Biochem. J., **28**:1550-1560. 1934.
13. Green, D. E., and Dixon, M. Studies on Xanthine Oxidase. XI. Xanthine Oxidase and Lactoflavine. Biochem. J., **28**:237-243. 1934.
14. Kensler, C. J., Sugiura, K., Young, N. F., Halter, C. R., and Rhoads, C. P. Partial Protection of Rats by Riboflavin with Casein against Liver Cancer Caused by Dimethylaminoazobenzene. Science, **93**:308-310. 1941.
15. Kinosita, R. Studies on Cancerogenic Chemical Substances. J. Japan Soc. Diseases Digestive Organs, **37**:513-592. 1938.
16. Miller, J. A., Miner, D. L., Rusch, H. P., and Baumann, C. A. Diet and Hepatic Tumor Formation. Cancer Research, **1**:699-708. 1941.
17. Mori, K., and Nakahara, W. Effect of Liver Feeding on Production of Malignant Tumors, by Injections of Carcinogenic Substances. Gann, **34**:48-56. 1940.
18. Nakahara, W., Mori, K., and Fujiwara, T. Effect of Liver Feeding on Experimental Production of Liver Cancer. (Preliminary Note). Gann, **32**:465-468. 1938.
19. Rosenberg, H. R. Chemistry and Physiology of the Vitamins. New York: Interscience Publishers, Inc. 1942.
20. Stern, K., and Willheim, R. Biochemistry of Malignant Tumors. Reference Press, Brooklyn, N. Y. 1943.
21. Strong, L. C. Chemical Studies on the Nature of Susceptibility to Spontaneous Carcinoma of the Mammary Gland in Mice. Yale J. Biol. & Med., **12**:255-268. 1940.
22. Strong, L. C. Chemical Studies of the Susceptibility to Spontaneous Carcinoma of the Mammary Gland in Mice. II. Indications for the Analysis of a Genetic Factor of Susceptibility in Relation to Nongenetic Influences. Arch. Path., **32**:420-424. 1941.
23. Sugiura, K., Rhoads, C. P. Experimental Liver Cancer in Rats and Its Inhibition by Rice-Bran Extract, Yeast, and Yeast Extract. Cancer Research, **1**:3-16. 1941.
24. Sugiura, K. Effect of Feeding Dried Milk on Production of Liver Cancer by *p*-Dimethylaminoazobenzene. Proc. Soc. Exper. Biol. & Med., **57**:231-234. 1944.
25. Watson, A. F. Tar Cancer in Mice Maintained on Diets Supplemented with Fresh Liver. Am. J. Cancer, **19**:389-395. 1933.

The Pathology of Malignant Histiocytoma (Reticuloendothelioma) of the Liver in Mice

P. A. Gorer, D.,Sc. M.R.C.P. (Lond.)

(From the Department of Pathology, Guy's Hospital Medical School)

(Received for publication February 25, 1946)

INTRODUCTION

Within recent years workers at the Roscoe B. Jackson Memorial laboratory have made frequent reference to reticuloendothelioma of the liver in mice (4), the growths occurring with a relatively high frequency in the C57 black strain (11). Representatives of this strain have been under observation here since 1934, but until 1940 only one growth of this type had been seen in more than a hundred autopsies on mice over 12 months old; since that date, however, they have become relatively common, the incidence in mice over 18 months of age being now of the order of 15 to 20 per cent, whilst sporadic cases have occurred in those of other strains. Apart from the spontaneous cases in the C57 strain, some have been induced precociously by the cutaneous application of 9,10-dimethyl-1,2-benzanthracene or methylcholanthrene. Details of this work will be published separately, but so far as the dimethyl compound is concerned it appears that a short course of painting with a 0.25 per cent solution is more effective in the induction of leukoses than is more intensive dosage.

The sudden change in the spontaneous incidence of these growths is probably associated with changes in diet necessitated by the war. During the same period hepatomas appear to have become rare in the CBA strain, as have certain renal lesions in the C57 strain. The principal modification was a change from Purina fox chow to Thorley's rat biscuits. In other respects it was not possible to keep the diet constant.

MATERIALS AND METHODS

This paper is based on a study of 11 spontaneous and 10 induced cases, 2 of the latter having been transplanted; these will be referred to as H.R.1[1] and H.R.2[1] respectively.

Materials for sections were fixed in neutral formol saline and stained with hemalum and eosin. Whenever possible impression-smears were made of the liver, and of other organs if the gross morbid anatomy appeared to justify it. Blood was generally obtained from the heart and from the tail. Blood and impression-smears were stained after air drying in a 5 or 10 per cent solution of Gurr's improved Giemsa stain buffered at pH 6.4 or 7.0. Blood and liver smears were usually well stained after 5 to 10 minutes at either pH; other tissues needed much longer, up to 2 hours in some cases, and it was found preferable to use the stronger solution at pH 7.0 in such cases.

"Normal" histiocytes were studied in sections and smears of inflamed lymph nodes, in the livers of mice with hepatitis, and in tumor-bearing mice with extramedullary myelopoiesis.

Transplantation was performed with liver emulsions, and except where stated to the contrary the emulsion was injected into the peritoneal cavity; the dose varied from about 1 to 6 million cells.

RESULTS

Morphological variations in nonmalignant histiocytes.—As seen in sections, murine histiocytes are usually somewhat darker than those seen in inflamed human lymph nodes, and in addition a nucleolus is less often seen in the former species; otherwise they resemble one another closely. A comparative study of the appearance in smears is being published elsewhere (7); here attention will be confined to the murine cells.

The histiocyte is most easily differentiated from the circulating leukocytes by means of its cytoplasm. With Romanowsky stains this is generally sky blue, and of a structure that might be interpreted as finely granular or as a foam with the stain adsorbed at the interfaces. Occasionally the cytoplasm is chromophobic, the stain being confined to the cell membrane. Cells with a dull blue cytoplasm are probably degenerate but an increased basophilism, where the color is a brilliant blue or greenish-blue, is indicative of a left shift. Under these conditions the structure may be coarser than normal, and filamentous bodies may be visible; the latter are almost certainly mitochondrial rods.

[1] H.R. = Hepatic reticulosis.

The nucleus is typically round or oval, and the ground color varies in different preparations from pink to deep mauve, with fine basophilic stippling; in addition there are usually one or two knots of chromatin and sometimes one or two chromatin threads. The mature cell generally has no visible nucleolus; the presence of such a structure is indicative of immaturity and is commonly accompanied by a modification of nuclear structure towards that commonly associated with blast cells.

It is by no means uncommon to find the nuclear structure resembling that of a lymphocyte. Since the size of the histiocyte may be anything from 6μ to 26μ it may be impossible to be certain of the identity of any particular cell, unless one is lucky enough to find a dwarf lymphocytoid histiocyte in the act of phagocytosis.

As it is now generally accepted that monocytes and histiocytes represent different functional phases of the same cellular type, it is not surprising to find forms morphologically intermediate between the two stages. However here one should stress, as Bloom (3) has done, that the nuclear differentiation of lymphocytes and monocytes is by no means so easy in mice as in man, and the differentiation of monocytoid and lymphocytoid histiocytes may be arbitrary in certain cases.

The Morbid Anatomy of Malignant Histiocytomas

The physical signs shown by a mouse with one of these tumors depends upon the fact that they may have ascites and subcutaneous edema, ascites alone, or hepatic enlargement without either. Cases are rather easy to miss; in the first instance the animal simply appears to be rather fat, whilst in the last it may have extensive pulmonary involvement before abdominal distention has become easily noticeable. Death is sometimes due to hemoptysis, hemorrhage into the peritoneal cavity, and presumably to hepatic insufficiency.

Edema fluid is always clear, whilst ascitic fluid may be clear, turbid, or contain blood.

The liver is enlarged to a variable extent, and in extreme cases may almost reach the pelvis. Its surface is finely granular and often shows yellow areas of infarction.

The spleen may be uniformly enlarged or nodular. In the former case (other than in the transplanted disease) it shows extramedullary myelopoeisis whilst the nodules are metastatic.

The mesenteric lymph nodes are sometimes considerably enlarged, as occasionally is the thymus; the superficial nodes are normal.

The lungs almost invariably have extensive hemorrhagic, edematous areas, but apart from this there are no macroscopic visceral abnormalities.

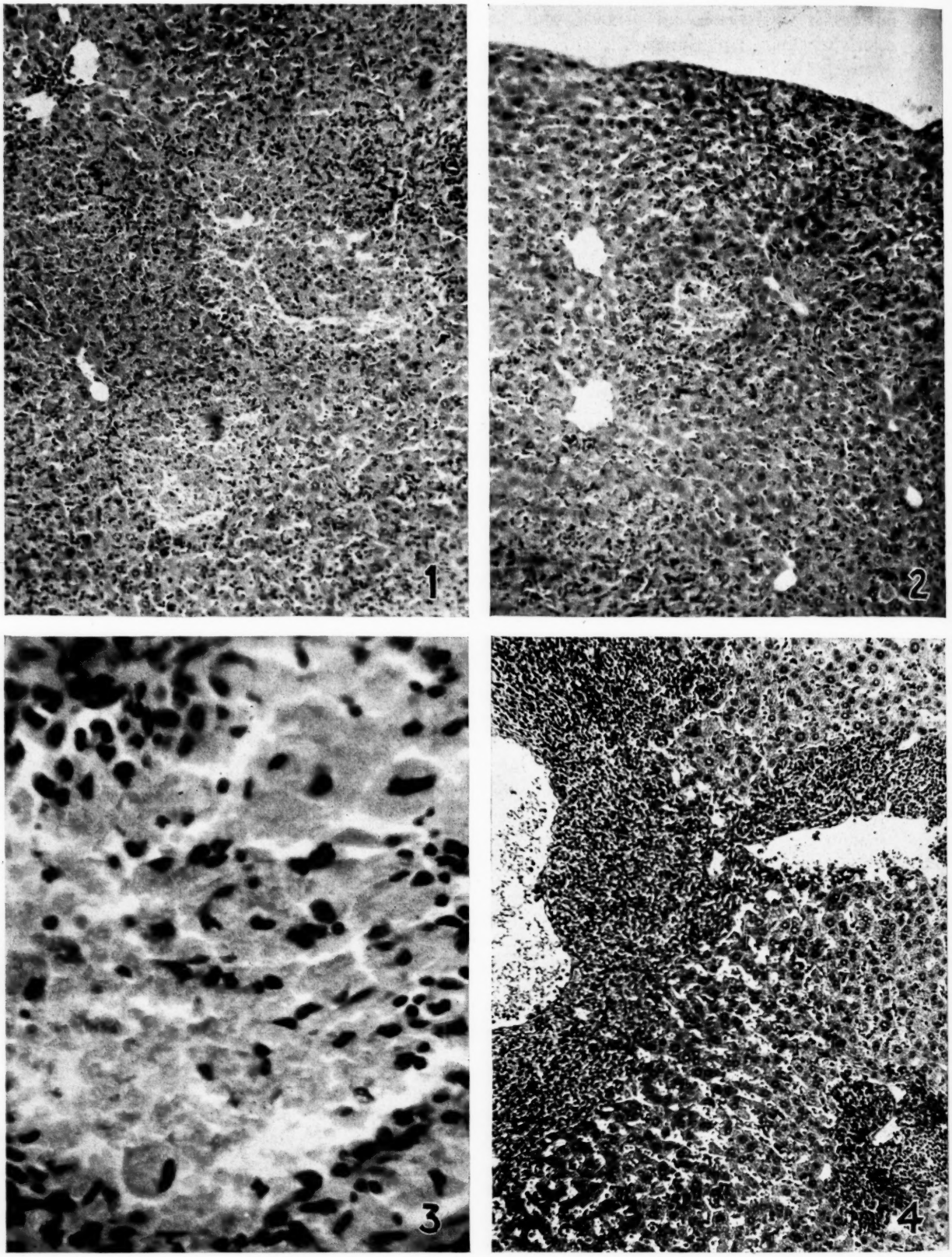
Morbid histology.—Inspection of early cases gives strong grounds for supposing that the growth is multicentric in origin (Figs. 1, 2), in which respect it resembles the malignant hepatomas and cholangiomas found in man. In this particular case the malignant cells showed exaggerated phagocytic activity, a feature shared by 3 other cases, which made these cells easy to pick out. Some of these hyper-phagocytic cells may be seen singly attached to the sinusoids, whilst there are large accumulations of cells scattered at random throughout the liver. There may be considerable hemorrhage in these areas, and some of the contents may be lost during the preparation of the sections. However, the random distribution of the main foci of proliferation makes the condition easy to differentiate from extramedullary myelopoiesis, which it resembles in macroscopic appearance. In the latter condition the main foci of proliferation are almost invariably round the larger blood vessels and the sinusoids are invaded secondarily from them (Fig. 4). Ultimately the whole liver becomes invaded, with the sinusoids grossly distended, but the larger foci of proliferation usually remain visible. Circulatory disturbances in the organ give rise to the areas of infarction and to the granularity. The latter is produced by distention of the sinusoids, with considerable destruction of the hepatic parenchyma. Hemorrhage may occur from such areas, which appear not unlike an angioma (Fig. 5).

The method of spread may also be seen in sections, including massive invasion of the hepatic veins and embolic invasion of the lymphatics. In the latter case, spread is presumably retrograde to the mesenteric lymph nodes and spleen (Figs. 6 to 9).

The appearance of the malignant cells varies in detail from case to case, and in different areas of the same liver. Cells invading the veins or lymphatics seldom contain much phagocytosed material regardless of the behavior of those in the liver as a whole. In only one case were the cells apparently primitive, and in another grossly aberrant cells were numerous. In all the rest the dominant cell was a mature histiocyte, variation affecting mainly the depth of staining and the degree of phagocytic activity shown.

A puzzling complication is the occurrence of considerable myeloid infiltration in certain cases; here reliance must be placed upon the behavior of the histiocytes and on the merits of the case as a whole (Fig. 6).

The spleen sometimes shows nodular accumulations of histiocytes, which may tend to invade the pulp. In the lymph nodes the malignant cells may be confined to the sinusoids, but if the pulp is invaded they become packed together and the appearance is that of a spindle-cell sarcoma. This appearance was first seen in an induced case (the origin of H.R.1), and it was natu-



FIGS. 1 and 2.—Foci of proliferation in early spontaneous case of malignant histiocytoma with hyper-phagocytic cells. Note that they have no tendency to be related to the larger blood vessels. The focus in Fig. 2 is far removed from those shown in here. Mag. × 100.

FIG. 3.—High power view showing hyper-phagocytic cells. Mag. × 600.

FIG. 4.—Extramedullary myelopoiesis in liver of mouse with induced skin cancer. Note concentration of areas of proliferation around the larger blood vessels. Mag. × 100.

rally thought that one was dealing with multiple induction (Fig. 10). However, since that date a spindle cell area has been observed in the liver in one case, and the transplantation experiments have made it certain that histiocytic tumors may assume this appearance. If spindle cell areas are smeared the cells spread out, very few maintaining their original shape (Fig. 11). It is of interest to record a male patient described by Baumgarten (1), apparently with monocytic leukemia, who had generalized spindle cell sarcomas of the lymph nodes.

In other viscera metatases are usually visible as intravascular emboli. Their presence in the lungs is invariable in all mice that die of the disease, and is often accompanied by hemorrhage into the alveoli. They may be found in almost any viscus, but their distribution is inconstant.

Blood picture.—In most cases the only feature in common between blood from the tail and that from the heart are indications of anemia.

(a) *Tail blood.*—The picture here is extremely variable. Quantitatively the white count may be normal. One usually sees a certain number of mononuclears that one suspects of malignancy, and a prolonged search may reveal an obviously malignant histiocyte. A polymorphonuclear leukocytosis is by no means uncommon, and this may be accompanied by a monocytosis. For example, in one case there were 15,000 white cells, of which 7,500 were polymorphonuclears, 2,500 lymphocytes, and 5,000 "monocytes." Some of the latter were phagocytic and others were in mitosis. In 3 cases a true monocytic leukemia occurred.

(b) *Heart's blood.*—Blood obtained by cardiac puncture at autopsy, and perhaps in life, generally comes from the right ventricle. Fekete (6) found that in normal mice the leukocyte count was generally lower in the heart's blood than in blood from the tail. This is not true of a number of pathological conditions. Here it is always possible to find numbers of histiocytes, some lying singly whilst others are in embolic clumps (Fig. 12). Histogenous mast cells may be present, and young myeloid cells may be more frequent than in the tail blood.

The appearance of liver smears.—There is no criterion that will enable one to identify a given cell as certainly malignant; the picture must be judged as a whole. However a brilliantly staining cytoplasm, a coarse structure, and hyper-phagocytosis are all strongly indicative. In typical cases the smear will contain very little besides histiocytes and the remnants of hepatic cells, the isolated nuclei of which are leptochromatic with coarse chromatin aggregations and several nucleoli; they might be mistaken for primitive or aberrant histiocytic nuclei. The cytoplasm, when present, is deeply basophilic and of a spongy texture.

Difficulty in diagnosis may arise if there is an accompanying myelosis, when inflammatory conditions may be closely mimicked. The above criteria will be found useful, but in addition one should look for large masses of histiocytes. Syncytial masses of these cells may occur in infections, but not to such an extent as in neoplastic conditions.

The histiocytes are somewhat pleomorphic and a few histioblasts may be present, but as a general rule the cells are mature and conform on the whole to a given type. A few multinucleate cells may be generally found, and these are often of the Reed-Sternberg binucleate type. In one case only were very aberrant hyper-phagocytic giant cells numerous. The original cases of H.R.1 and H.R.2 are good examples of the general run. In the first the bulk of the nuclei were of monocytoid or lymphocytoid type, the cytoplasm being typically histiocytic and brilliantly basophilic (Fig. 13). In H.R.2 there was considerable myeloid reaction, and considerable inflammatory change affecting the larger blood vessels. The histiocytes were fairly normal in appearance, but were hyper-phagocytic (Figs. 6, 7, 14). The latter, in conjunction with the presence of emboli in the heart's blood, determined the diagnosis and enabled transplantation to be undertaken with confidence.

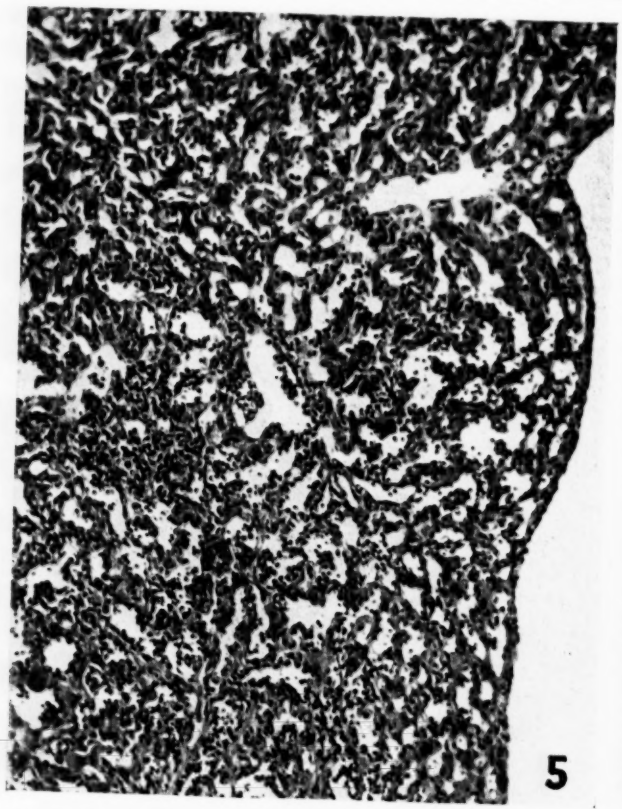
Transplantation experiments. (*a*) *H.R.1.*—Table I shows the general modifications undergone by H.R.1 following routine intraperitoneal inoculations for the first 20 transfers. Reference to the results of subcutaneous transfers made at the second, fourth, fifth, tenth, and 11th passages will be made later. Since the 20th transfer all inoculations have been subcutaneous.

It will be seen that the tumor underwent 3 morphological phases and 4 phases in growth rate.

The gross morbid anatomy during the first 2 transfers was very similar to that of a spontaneous case, there being very little evidence of cellular proliferation in the peritoneal cavity or mesenteries and the liver being enlarged and diffusely infiltrated. The cells were perhaps somewhat larger than in the original case, and lymphocytoid forms were less numerous.

From the third to the 15th transfer there was considerable cellular proliferation in the mesenteries, with large aggregations of malignant cells in the pelvis and on the surfaces of the viscera. The intestines tended to be matted together, the whole picture suggesting a plastic peritonitis. The liver generally showed numerous discrete metastatic nodules, although occasionally it was diffusely infiltrated.

Histologically the great bulk of the extrahepatic deposits were spindle cell sarcomas, with occasional giant cells that were often of the Langhans type. Some deposits were round cell sarcomas of the "reticulum" cell type. Spindle cell areas were rare in the liver.



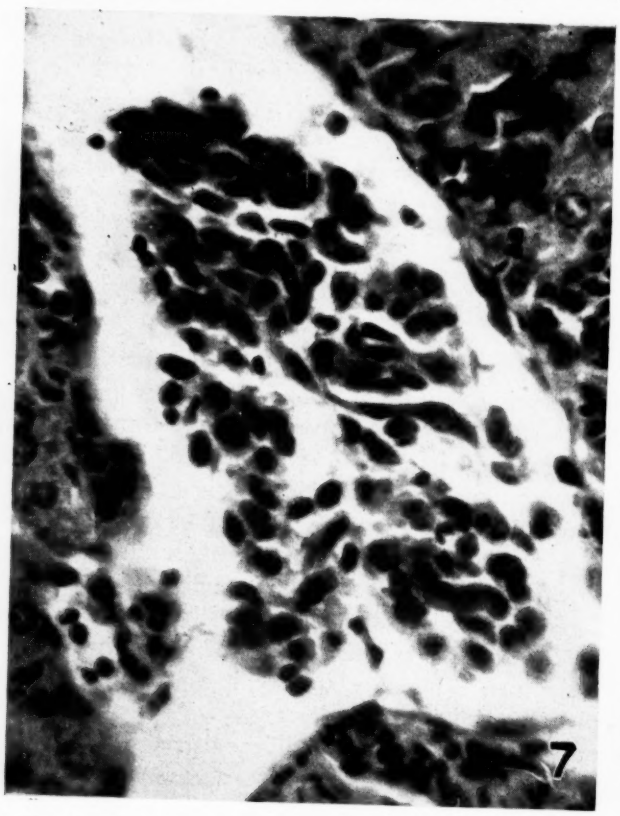
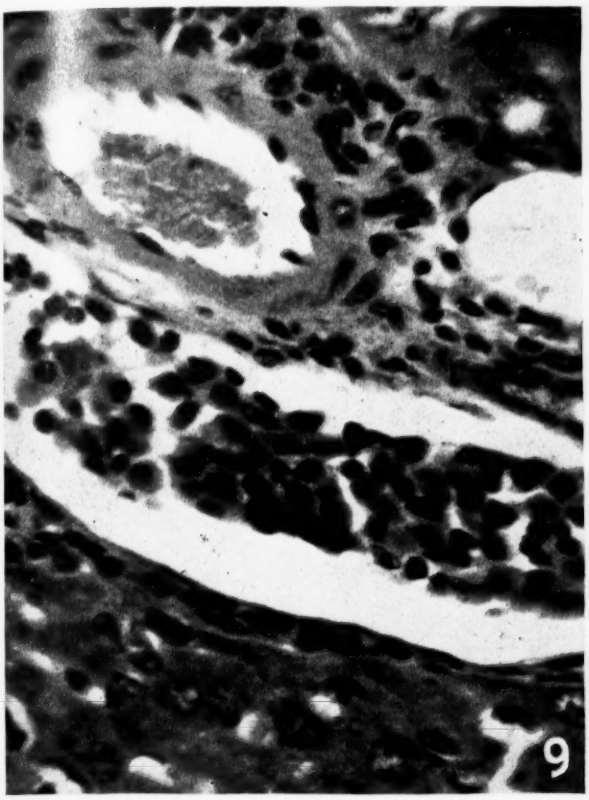


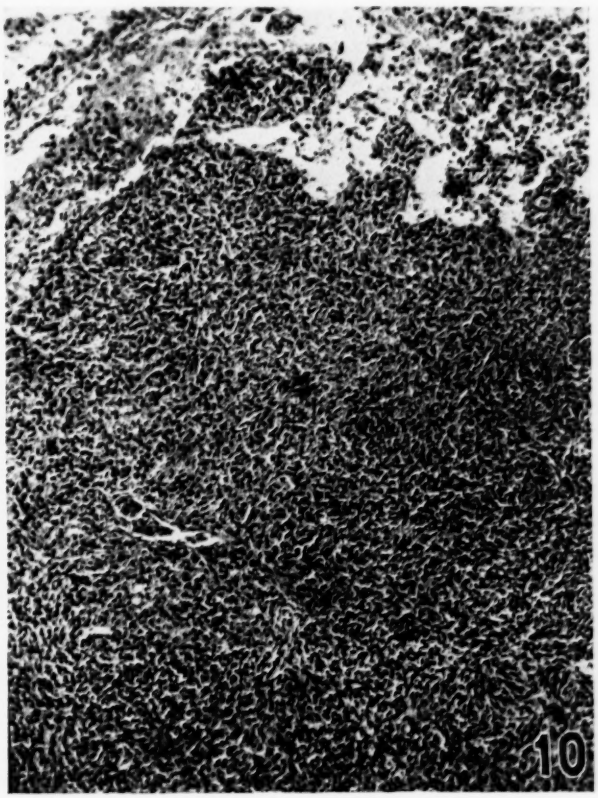
FIG. 5.—Dilatation of sinusoids in spontaneous case. Note angiomatous appearance, but (top right) that one of the sinusoids communicates with a hepatic vein. Same case as Fig. 12. Mag. × 100.

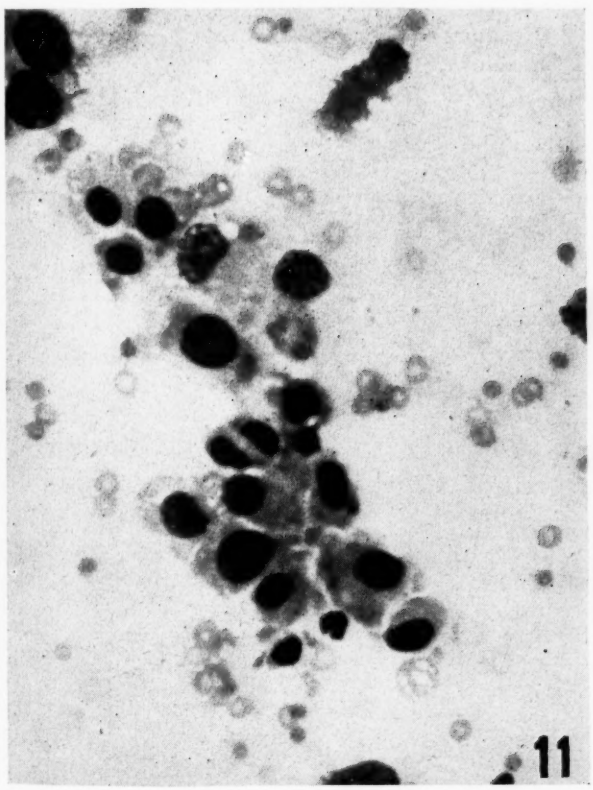
FIG. 6.—Induced case, origin of H.R.2. Extra-medullary myelopoiesis, plus malignant emboli in veins. Mag. × 100.

FIG. 7.—High power view of malignant embolus in origin of H.R.2. Compare with Fig. 22. Mag. × 600.

FIG. 8.—Induced case, origin of H.R.1. Note absence of myelopoiesis, emboli in lymphatics (bottom left) and vein (top right). Mag. × 100.







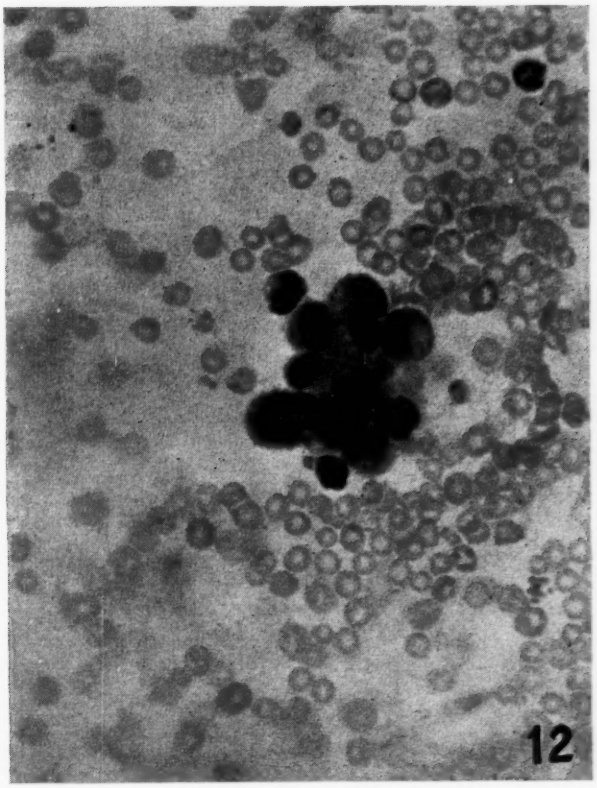
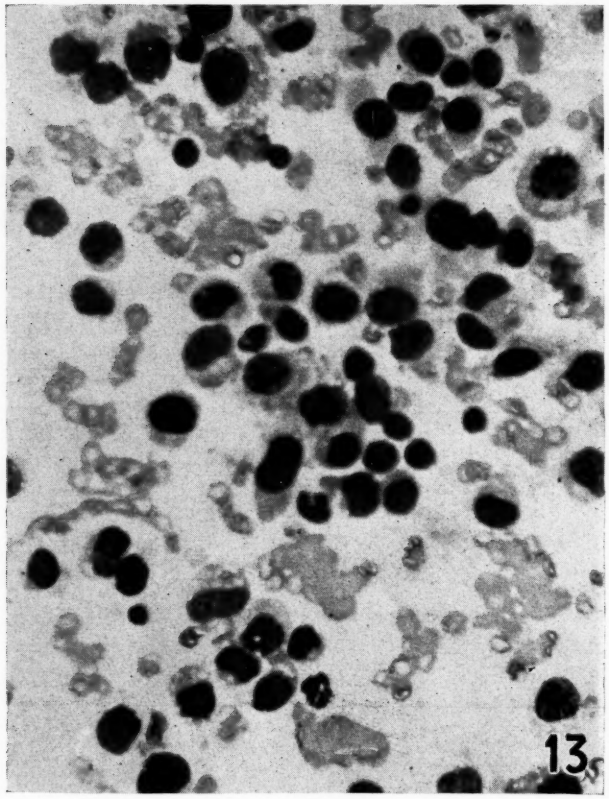


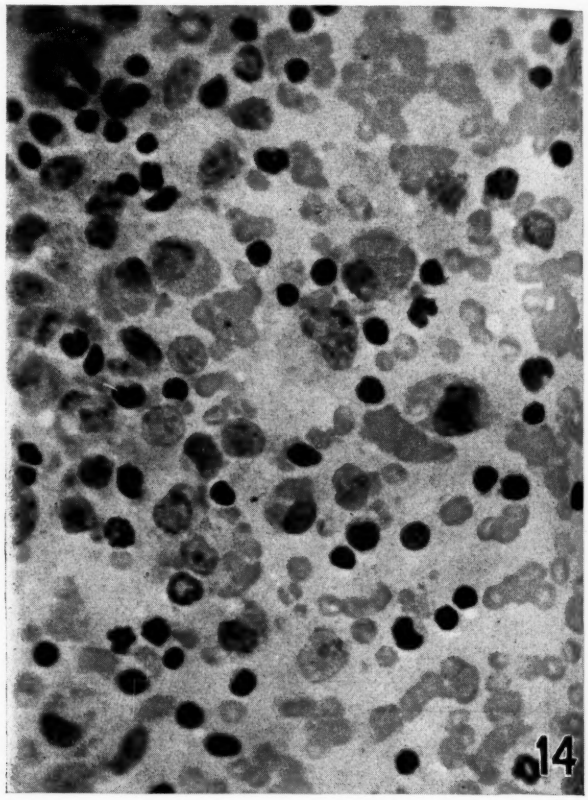
Fig. 9.—High power view of lymphatic embolus. Compare with Figs. 10, 15-18, and 20. Mag. × 600.

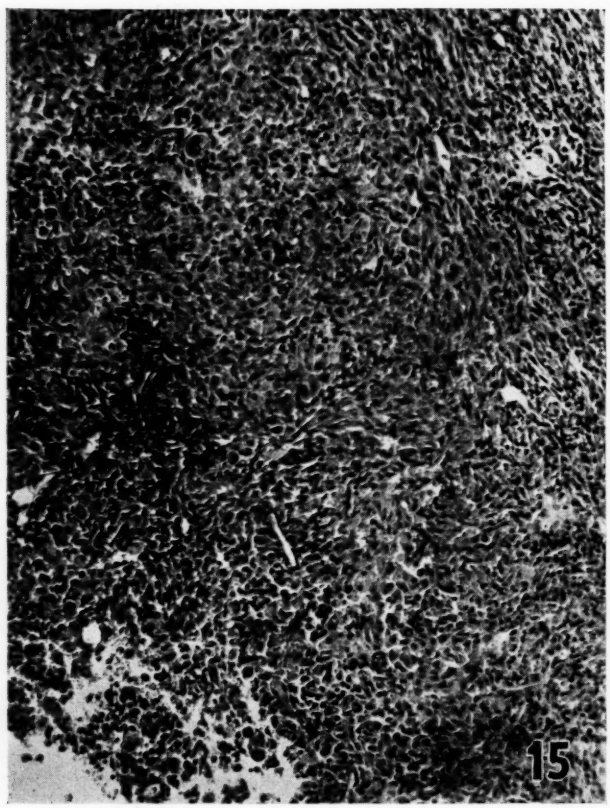
Fig. 10.—Spindle cell metastasis in mesenteric lymph node of case above. Mag. × 100.

Fig. 11.—Smear from spindle cell metastasis of transmitted case (H.R.1, tenth transfer). This is the usual appearance; few cells retain the spindle form. Same case as Figs. 15 and 16. Mag. × 600.

Fig. 12.—Malignant embolus in heart's blood of spontaneous case. Mag. × 600.







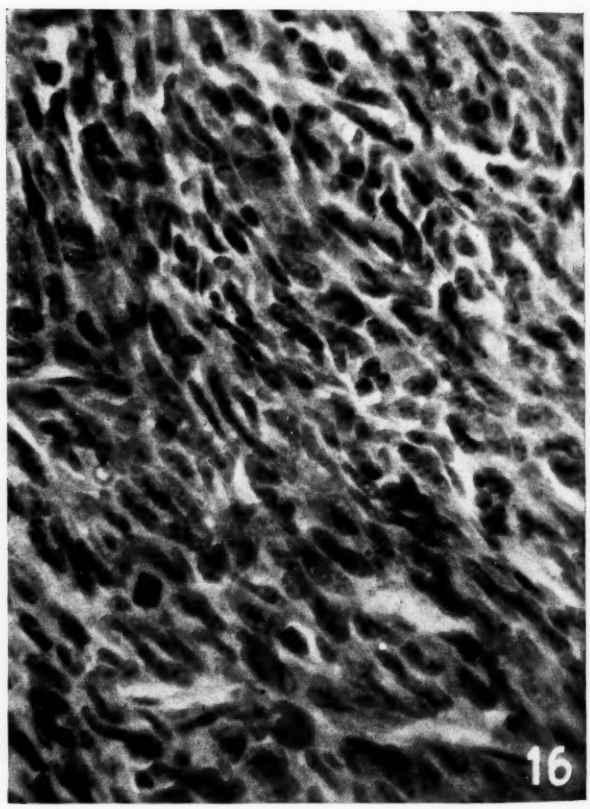


FIG. 13.—Liver smear from origin of H.R.1. Cells tend to have dark "lymphocytoid" nuclei. Some were phagocytic. Mag. × 600.

FIG. 14.—Liver smear, origin of H.R.2. Histiocytes fairly normal in appearance. Several contain ingested red cells, including one small lymphocytoid cell near center. Mag. × 600.

FIG. 15.—Spindle cell sarcoma, subcutaneous implant, H.R.1, tenth transfer (see Fig. 11). Mag. × 100.

FIG. 16.—High power view of spindle cell tumor. Mag. × 600.

Generally the histiocytes were large and bloated, but of epithelioid or "reticulum" cell form. Multinucleate cells were fairly numerous. There was a considerable tendency towards a diffuse infiltration of the sinusoids, the metastatic nodules being less discrete than appeared macroscopically (Figs. 15-19).

Embolic metastases were always seen in the lungs, and in late cases in almost every organ in the body.

In liver smears it could be seen that a number of the cells were extremely aberrant. There was considerable anisocytosis; the nuclei were somewhat dark and generally contained 3 or 4 nucleoli, around which were coarse aggregations of chromatin. Multinucleate cells and cells with very bizarre nuclei were far commoner than one would deduce from a study of sections.

ent from that seen following intraperitoneal inoculation. At the tenth transfer the general picture was similar, but the subcutaneous tumors were about 1.0 cm. in diameter.

The drop in growth rate that occurred subsequent to the second transfer may not be entirely due to a diminished rate of cell division; involvement of the peritoneum would tend to produce symptoms less rapidly than when cellular proliferation was occurring in the liver. The acceleration of growth that occurred at the 11th transfer was not accompanied by any obvious anatomical change. At the 16th transfer a sudden and dramatic transformation occurred when the growth took on the morphology of acute leukemia.

Diffuse infiltration of the peritoneal tissues disap-

TABLE I: THE CHANGES UNDERGONE BY H.R.1 FOLLOWING INTRAPERITONEAL INOCULATION

Transfer no.	No. of mice	Days of death	Anatomical notes
1	5	K35,36. D.35,39(2),52.	Similar to spontaneous case.
2	3	K.27,27-33.	Diffuse enlargement of liver.
3-10	50	D.39-95 (Median 61)	Malignant plastic peritonitis. Metastases in liver. Extrahepatic deposits, spindle cell sarcoma.
11-15	20	D.16-48. (Median 26)	As before.
16 and on.		D.14-30 (Variable, depending on dose and age of mice)	Acute leukemia. Small primitive cells.

K = killed.
D = died.

Myelopoiesis in the liver was of sporadic occurrence. At the seventh transfer there was a diffuse infiltration with eosinophils, which had not been seen before and has not been observed since.

The blood picture was variable, probably depending in part on the stage of the disease at which an examination was made. A true leukemia was never seen, but the tail blood might contain as many as 5,000 "monocytes" per cu. mm. out of a total of 15,000 leukocytes.

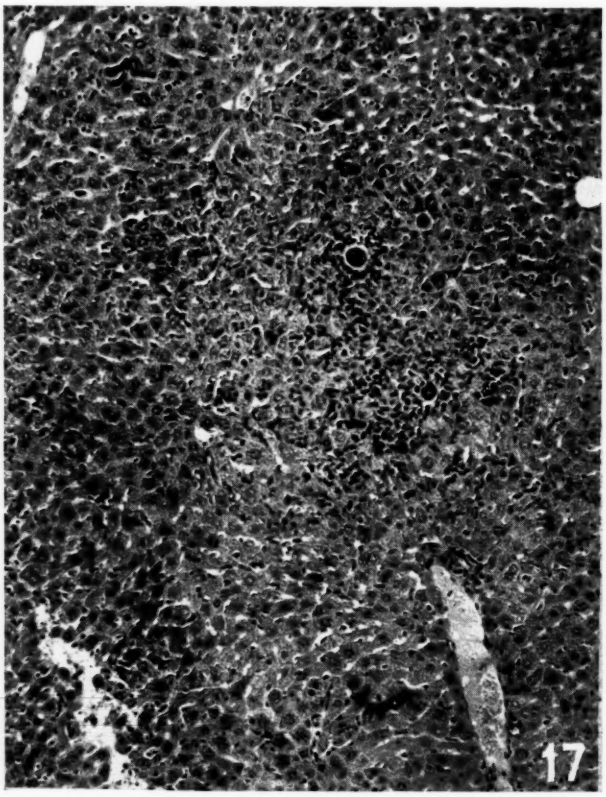
The results of subcutaneous inoculation were very unreliable; in some cases death occurred as rapidly as with the alternative route, but 5 mice inoculated at the tenth transfer on January 2, 1945, are still symptom-free more than 1 year later. Prior to the tenth transfer the subcutaneous deposit was often invisible during life, and was never more than a minute papule. The regional lymph nodes were very slightly enlarged, and on section the malignant cells seemed concentrated in the sinuses. They were large and well spread out, whilst the small subcutaneous papule might be spindle celled. The picture is very reminiscent of that described by Parsons (1938), which seemed to indicate possible tumor induction in the lymph node by some extracellular agent. The liver was greatly enlarged, and the ultimate course of the disease was little differ-

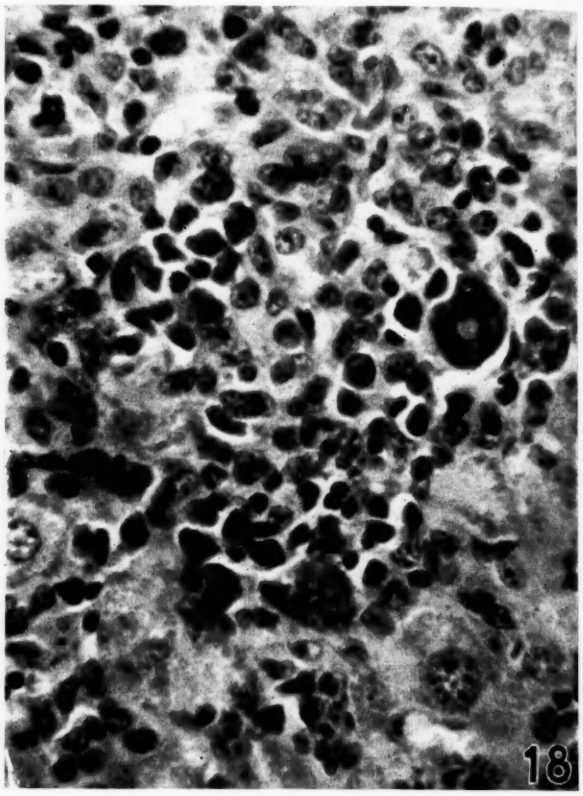
peared completely. There was gross enlargement of the liver and spleen, and generalized enlargement of the lymph nodes. The cellular picture was that of a blast cell leukosis, and one who did not know the history of the case might consider it a lymphoblastic leukemia. A number of the cells were hypoploid, and one with only 16 chromosomes was seen (Figs. 20, 21).

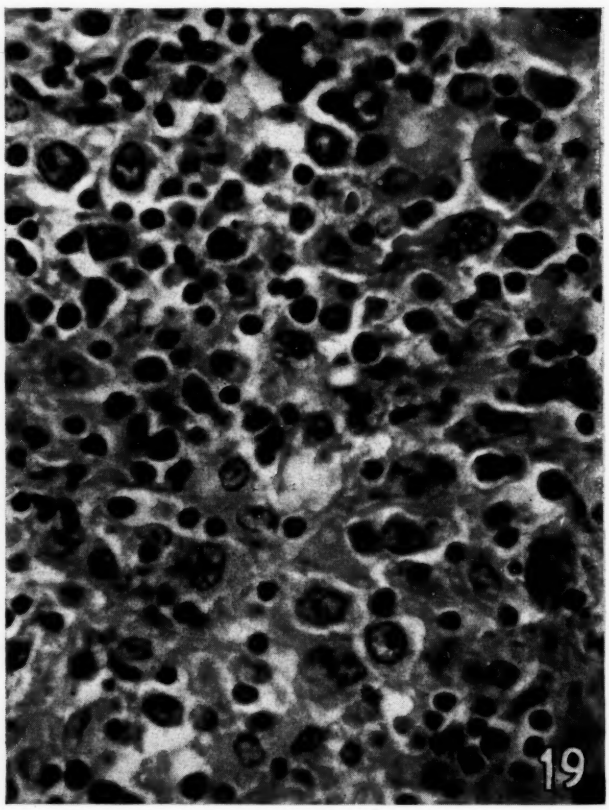
Differentiation can still occur to some extent (Fig. 21). It occasionally may be seen in the diffuse deposit one may get following subcutaneous transmission, where many bizarre forms may be seen. In liver smears small monocytoid histiocytes seem to occur fairly regularly. Transitions between these and the histioblasts can be made out. Differentiation perhaps occurs following an abortive mitosis. The kidney shaped nucleus being constituted round the metaphase chromosomes (9).

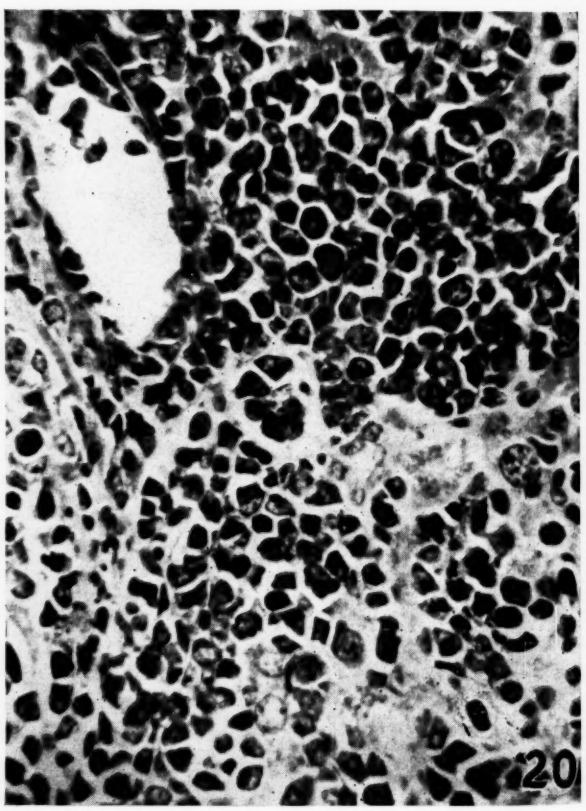
The cell count in blood from the tail is as a rule grossly raised only towards the end of the disease, when it may be 100,000 or more, but a few primitive cells may be generally found much earlier.

The dose has been reduced to about 100,000 cells, administered subcutaneously, in an effort to prolong life and economize in mice. However, in the most recent transfers the disease seems to have gained slightly in virulence and generally kills in from 14 to





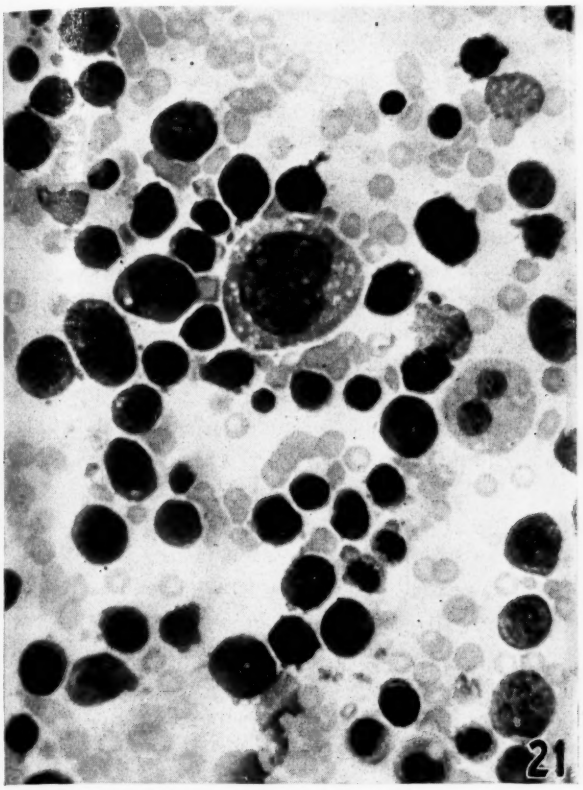


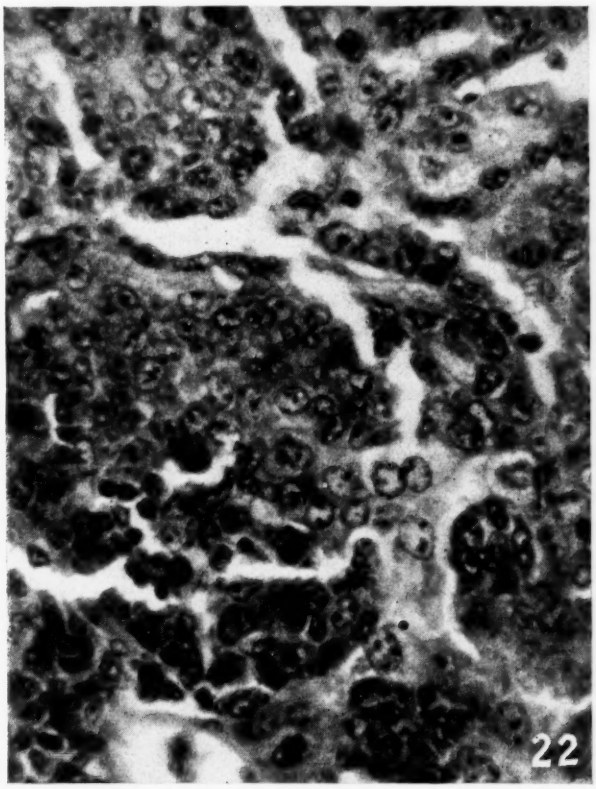


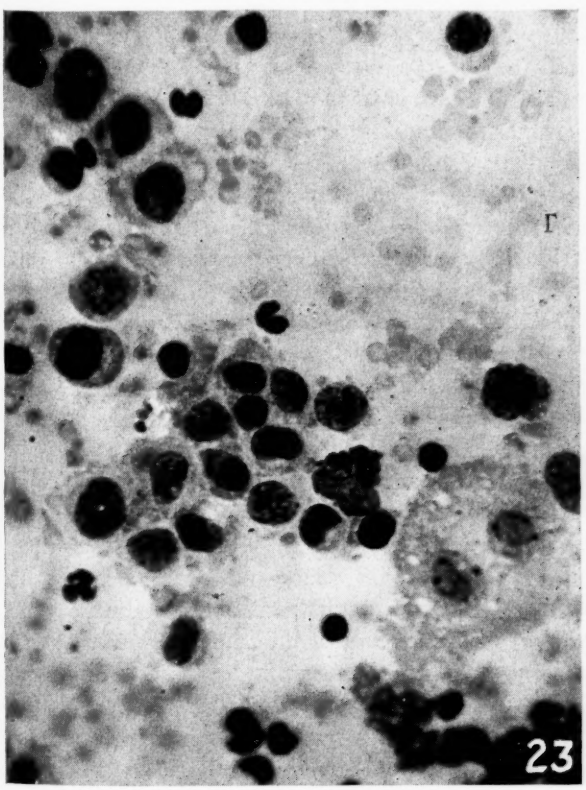
FIGS. 17 and 18.—Hepatic metastases from tumor in Figs. 15 and 16. Giant cells were seldom so numerous as this in H.R.1, but were more often abundant in H.R.2. Mag. × 100 and × 600.

FIG. 19.—Hepatic deposit, Hodgkin's disease (human), to compare with Fig. 18. Mag. × 600.

FIG. 20.—Appearance of liver in H.R.1 from 16th transfer on. Compare with Figs. 8, 9, and 17, 18. Mag. × 600.







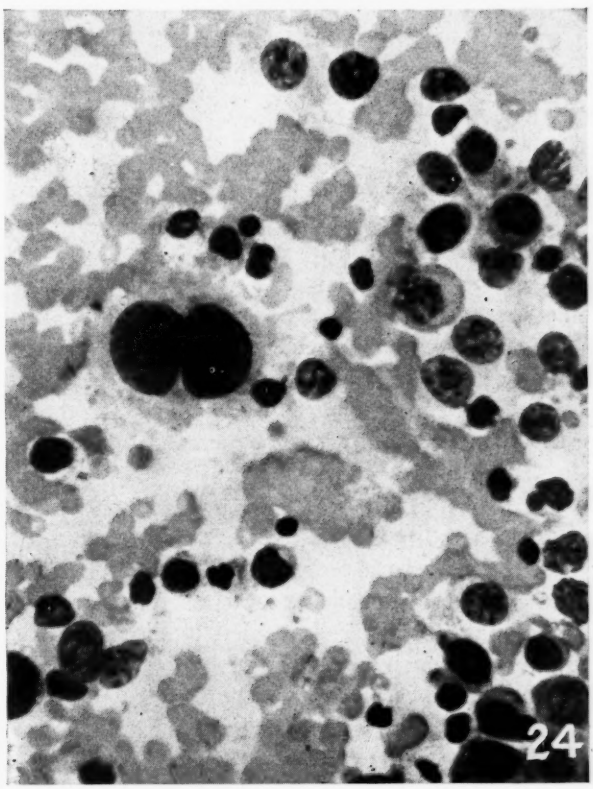


FIG. 21.—Liver smear, H.R. 1, 16th transfer. Cells so dark that nucleoli do not show up well. Two aberrant histiocytes may be seen; most of the cells look like lymphoblasts. Blood was leukemic. Mag. × 600.

FIG. 22.—Liver of H.R.2, sixth transfer. Note that cells have morphology of "reticular" or germinal center cell, with vesicular nucleus and prominent nucleolus. In smears many show mature histiocytic cytoplasm. Compare Figs. 7 and 23. Mag. × 600.

FIG. 23.—Smear from liver of H.R.2, sixth transfer. Difference between histioblastic and mature cytoplasm readily appreciated by comparing dark cell at left center with those of central clump. Nucleoli can be made out in most of latter; they are particularly prominent in large binucleate cell at right bottom. Compare Figs. 13 and 14. Mag. × 600.

FIG. 24.—Smear from liver, H.R.2, 13th transfer. Reed-Sternberg giant cell, with great anisocytosis amongst other histiocytes. Mag. × 600.

17 days. It still remains specific for the C57 black strain.

(*b*) *H.R.2.*—Table II shows that with this tumor there was a progressive increase in virulence for the first 4 transfers; thereafter the behavior remained fairly constant until the tenth, when the growth rate fell and has since remained low but variable, like the middle period of H.R.1.

During the first 10 transfers the lesions were mainly concentrated in the liver, which was generally diffusely enlarged.

In the first 3 transfers there was considerable ascites. At the fourth passage this was diminished, but there was a striking tendency to hemorrhage.

From the 12th transfer onwards there has been a transfer, and there still seemed to be a greater tendency for malignant cells to enter the peripheral circulation than was the case during the middle period of H.R.1.

Histologically the extrahepatic deposits are usually spindle celled, together with numerous giant cells of various types; they are seen more often than with H.R.1.

Subcutaneous inoculations were performed at the third and fourth transfers. The results were anatomically similar to those obtained with H.R.1, but the time of death was even more delayed. Thus following intraperitoneal inoculation at the fourth transfer death occurred between the 24th and 27th days, whilst 3 mice inoculated subcutaneously died between the 87th and 89th days.

TABLE II: THE CHANGES UNDERGONE BY H.R.2 FOLLOWING INTRAPERITONEAL INOCULATION

Transfer no.	No. of mice	Days of death	Anatomical notes
1	5	K.102(2). D.113(2).119.	Similar to spontaneous case. Progressive left shifts in cells.
2	4	K.42,49. D.48,49.	
3	4	K.26,48,51. D.48.	Transition gradual to next stages.
4-11	32	D.27-37(11th transfer). Median (24).	Cells more invasive. Most lesions in liver. Invasion of diaphragm. Giant cells more numerous towards end of period.
11-17	40	D.37-137. (Median 75).	Plastic peritonitis. Generally similar to H.R.1.

K = killed.
D = died.

malignant plastic peritonitis similar in appearance to that described in H.R.1.

During the first 3 transfers there was considerable diminution in the myelopoiesis compared with the original case, as there was in phagocytic activity. During the period of maximum activity the picture was more that of a round cell sarcoma or an acute blast cell leukosis (Fig. 22). A feature of this period was direct invasion of the thorax by way of the diaphragm, with the formation of deposits on the heart.

Liver smears of the first transfer showed many lymphocytoid and monocytoid forms. From then until the fourth there was a progressive left shift that was perhaps even more notable at the sixth transfer. The nuclei of many of the cells tended to resemble that commonly described for the large lymphoblast (Fig. 23). In some the cytoplasm was undifferentiated, but in most it was of histiocytic structure and a fair number of cells were phagocytic.

From the eighth transfer on bizarre forms became increasingly numerous and there seemed to be a general increase in cell size accompanied, however, by extreme anisocytosis (Fig. 24).

A true leukemic blood picture was seen at the sixth

DISCUSSION

The term "reticuloendothelial system" was first coined by Aschoff to denote the system of fixed phagocytic cells. If this conception is retained the histiocyte becomes the reticuloendothelial cell par excellence, and the name of reticuloendothelioma becomes perfectly suitable for the growths described here. However, most modern workers regard this system as the origin of the blood cells, plasma cells, and histiocytes, and therefore postulate a primitive reticulum cell of wide developmental potencies. In this case it seems preferable to define proliferative lesions of this system by the dominant cell series where one can, or else to use a term such as reticulosarcoma, which indicates the system involved without commitment to any theory concerning it.

The morphology of the reticular stem cell is uncertain. In some writings it is apparently the same as the histiocyte, whilst others follow the teaching of Maximov (12), who postulated two cellular types attached to the reticular syncytium: a small multipotent cell, and fixed histiocytes. The ordinary blood cells are apparently desquamated from the syncytium in a primitive state as the recognized blast cells. The evi-

dence obtained from a study of the tumors H.R.1 and H.R.2 gives evidence that the same can occur with the histiocytes. The first has reverted fairly completely to a primitive cell, whilst the second went far towards it. This hypothesis has been further re-inforced by a study of impression smears of human lymphadenopathies. The easiest to interpret are those obtained from certain patients with chronic erythrodermia or exfoliative dermatitis. Inspection of sections make it clear that the great bulk of cells are histiocytic. In smears one can see numerous large primitive cells together with transitions between these and mature histiocytes. It seems logical to refer to the former as histioblasts. The present writer is unconvinced by the accepted morphological criteria for distinguishing primitive cells as individuals. Histioblasts look very like lymphoblasts, but are usually larger.

If we accept Maximov's conception of the two types of reticular cell reticuloendotheliomas might be of two kinds. In one the stem cell might proliferate without differentiation, whereas in the other there would be some tendency towards the formation of certain of the definitive forms. There is no certain record of either of these types. Of the connective tissue tumors occurring in the human liver we have the simple cavernous hemangioma and the rare hemangioendothelioma, and sarcomatous types (2, 8). The second of these are vasoformative and hemopoietic, sometimes producing histiocytes (Jaffé). The last are often spindle-celled, but some are certainly histiocytic and form the nearest approach to the murine growths. Pullinger (15) considers it possible that Hodgkin's disease is a reticuloendotheliosis, the causative agent acting directly on Maximov's stem cell and stimulating it to form the various cellular types found. This may be so, but elsewhere the present writer has given reasons for believing that the bulk of the swollen "reticular" cells are histiocytes in varying stages of differentiation (7) (Figs. 17-24).

There seem good reasons for exercising great caution in the use of the term reticuloendothelioma, but it is far less easy to decide between the merits of histiocytoma and monocytoma. The latter term was used by M. R. Lewis (10), to describe a tumor chemically induced in the spleen of a mouse of the C57 black strain.[2] Histologically it was described as having the appearance of a tubercle that had become malignant, except that occasional multinucleate cells had the appearance of Reed-Sternberg cells rather than that of the Langerhans type. It is generally agreed that monocytes can develop into epithelioid cells and Langerhans cells, so that the terminology is perfectly logical and has the additional attraction of simplicity. Amongst the hepatic tumors studied here there were a certain number in which cells with a monocytic type of cytoplasm were quite as common as, or commoner than those with a histiocytic type, which would appear to supply an additional argument in favour of Lewis's terminology. However, a typical histiocyte is recognizably different from a monocyte, and the presence of one of the former in the blood stream would be regarded by clinical hematologists as definitely abnormal. Similarly in human pathology there are a number of reticulosarcomas that are probably histiocytic, though the lymph nodes are recognizably different from those in monocytic leukemia of the so-called Naegeli type. In the Schilling type of monocytic leukosis the present author regards the dominant cell as a histiocyte rather than a primitive reticuloendothelial cell (5, 7), the condition being closely allied to the murine hepatic neoplasms with a leukemic or subleukemic blood picture and probably to the reticuloendotheliosis described by Mider and Morton (13). However, in human pathology one may meet with cases in which it is entirely a matter of personal choice whether to speak of a histiocytosis or a monocytosis. Only future experiments can show whether it is advantageous to retain both terms, or to adopt the simpler alternative offered by Lewis.

[2] A spontaneous growth of identical histological appearance was found arising in the lower ileum of a mouse of the same strain whilst the author was at the Lister Institute. Unfortunately it was not transplanted.

SUMMARY AND CONCLUSIONS

1. Histiocytomas of the liver have been principally studied in the C57 black strain of mice. They occur spontaneously in mice upwards of 18 months old, but may occur considerably earlier in those treated with carcinogenic hydrocarbons.

2. The growths are apparently of multicentric origin, arising in the sinusoids. Extramedullary myelopoiesis, which may accompany them, is generally perivascular in origin.

3. A description of nonmalignant histiocytes is given. Forms intermediate between histiocytes and monocytes may be found, whilst the nuclear structure may often resemble that of a lymphocyte.

4. Impression smears of the liver show that the dominant cell is a functionally mature histiocyte.

5. The heart's blood generally contains large numbers of malignant histiocytes.

6. Blood from the tail gives a variable picture; a few malignant cells probably occur in all late cases, but a true leukemic blood picture is exceptional.

7. Histiocytomas may have the morphology of a spindle cell sarcoma, particularly in metastases or on transplantation.

8. Two cases (H.R.1 and H.R.2) have been transplanted. In the earlier transfers both showed a definite tropism for the liver.

9. Both have undergone fluctuations in virulence.

10. Once the tropism for the liver was lost they produced a malignant plastic peritonitis with metastases. The peritoneal deposits were spindle-celled. Giant cells occurred occasionally in H.R.1, but more abundantly in H.R.2.

11. H.R.1 now has the characteristics of an acute leukemia. The dominant cell is small and primitive, resembling a lymphoblast. It has retained some power of differentiation.

12. During its period of most rapid growth the cells of H.R.2 showed certain primitive features, particularly in nuclear structure. On one occasion during this period the tail blood showed the picture of a monocytic leukemia.

13. The question of the terminology of neoplasms of reticuloendothelial origin is discussed.

14. It is concluded that the histiocyte is derived from the primitive reticular cell of Maximov through an intermediary histioblast.

ACKNOWLEDGMENTS

The upkeep of the mice used in these experiments was defrayed by a grant from the Lady Tata Memorial Trust. The author is indebted to Professor G. P. Wright for his interest in the investigation, and to his colleagues on the clinical staff for their help in obtaining material for comparative study.

REFERENCES

1. Baumgarten, v. P. Primäres generalisiertes Spindelzellsarkom der Lymphdrüsen. Berlin Klin. Wchnschr., **52**: 1201-1205. 1915.
2. Blondel, E. Le Tissue Reticulo-Endothélial du Foie et ses Tumeurs Malignes. Libraire Le François. Paris, 1933.
3. Bloom, W. Lymphocytes and Monocytes. Handbook of Hematology, by H. Downey. Vol. I. New York: Hoeber and Company. Vol. 1. 1938, pp. 374-446.
4. Cloudman, A. M. A Transferable Liver Neoplasm (C198) Arising in a Female Mouse of the Leaden Strain. Am. J. Cancer, **36**:578-580. 1939.
5. Downey, H. Monocytic Leucemia and Leucemic Reticuloendotheliosis. Handbook of Hematology. Vol. II. New York: P. B. Hoeber, Inc. 1938, pp. 1274-1333.
6. Fekete, E. The Biology of the Laboratory Mouse. Chapter 3. Histology. Philadelphia: Blakiston Company. 1941, pp. 86-167.
7. Gorer, P. A. Morphological Variations in the Histiocytes of Mice and Men. Guy's Hospital Reports. In press. 1946.
8. Jaffé, R. H. The Reticulo-Endothelial System. Handbook of Hematology, by H. Downey. Vol. 11. New York: Hoeber and Company. 1938, pp. 973-1271.
9. La Cour, L. F. Mitosis and Cell Differentiation in the Blood. Proc. Roy. Soc. Edin., **62**:73-85. 1944.
10. Lewis, Margaret R. A Transmissible Monocytoma of the Mouse. Am. J. Cancer, **36**:34-43. 1939.
11. Little, C. C., Murray, W. S., and Cloudman, A. M. The Genetics of Non-Epithelial Tumor Formation in Mice. Am. J. Cancer, **36**:431-450. 1939.
12. Maximov, A. A. The Macrophages or Histiocytes. *In* Special Cytology, by E. V. Cawdry. Vol. II. New York: P. Hoeber, Inc. 1928, pp. 425-484.
13. Mider, G. B., and Morton, J. J. The Effect of Methylcholanthrene on the Latent Period of Lymphomotosis in Dilute Brown Mice. Am. J. Cancer, **37**:355-363. 1939.
14. Parsons, L. D. Changes in the Lymph Glands of Tumor-Bearing Mice. J. Path. & Bact., **47**:501-523. 1938.
15. Pullinger, Beatrice D. Histology and Histogenesis. *In* Rose Research on Lymphadenoma. Bristol: John Wright & Sons, Ltd. 1932, pp. 117-136.

American Association for Cancer Research, Inc.

37th Annual Meeting

Ambassador Hotel, Atlantic City, New Jersey
March 11 and 12, 1946

Proceedings of Scientific Sessions

THE BETATRON. THEODORE J. WANG. (Department of Electrical Engineering, Ohio State University, Columbus. Ohio.)

The betatron is an electron accelerator capable of producing beams of electrons and x-rays with energies very much higher than have been attainable in any machines up to the present time.

The betatron employs a modification of the principle of the voltage step-up transformer. In the betatron the primary winding of the transformer is retained, but the customary secondary winding is replaced by a doughnut-shaped evacuated chamber. Electrons injected into this "secondary" chamber are accelerated in transformer manner by the induced electric field, which is associated with the time-changing magnetic flux of the primary. The action differs from that of the conventional transformer in that in the betatron "secondary," electrons traverse repetitive circular paths in the evacuated space within the chamber; whereas in a transformer secondary, electrons are confined to within the successive turns of a metallic conductor. In the betatron the electrons are retained in a circular orbit as a result of a field-velocity interaction force (the same basic type of force as causes the whirling of ions in a cyclotron).

Low energy electrons are injected in bursts at the beginning of each flux cycle, and high energy electrons are removed, or caused to strike a target (to produce x-rays), at any desired phase up to the peak of the cycle. The acceleration period for 60 cycle operation is of the order of a hundredth of a second, during which time the circulating electrons travel a few hundred thousand revolutions within the chamber. Utilization of the beam is accomplished by momentarily upsetting those magnetic field conditions which make for stability of the orbit. A fresh burst of electrons is injected at the beginning of each cycle, and the process repeats in machine-gun fashion.

The x-ray beam is easily removed so as to be applicable for therapy, since the x-rays pass directly through the walls of the chamber unaffected by the magnetic field. As yet the successful complete removal from the chamber of the confined electron beam has not been announced, although the problem is being studied.

Interesting specific ionization properties are shown by the radiations of high energies that are obtainable from the betatron. *Electrons* of high energy exhibit ranges of approximately a centimeter of path in tissue-like material for each two million volts of energy, with nearly constant ionization per centimeter up to within the last few millimeters of their paths, where they ionize excessively. Specific ionization curves of *x-radiation* are due to the composite effects of (1) the characteristics of the decay of primary quanta through photoelectric, Compton, and pair-production processes, and (2) the ionization resulting from secondary electrons of various energies (up to the maximum of the x-ray beam), which are produced at various depths within the absorber. The net result of these superposed effects is that specific ionization curves for primary x-ray beams below a few million volts are essentially S-shaped; while for energies above 5 million volts the ionization curves show definite maxima at depths which are a function of the energy spectrum of the incident x-rays.

Associated with radiation of increased energy are (1) reduced angle of spread of beam, (2) reduced percentage of scattered radiation.

Photographs were shown of operating betatron installations and of commercially available models.

THE USE OF THE BETATRON IN CANCER THERAPY: A PREVIEW. HENRY QUASTLER. (Carle Hospital Clinic, Urbana Ill.)

In the radiation therapy of deep-seated tumors, we try to concentrate the energy absorption in the region occupied by the tumors. Every increase in topographic selectivity improves the results. High energy roentgen rays permit greater selectivity than the conventional rays of 200 to 1,000 kv. energy. Thus, the betatron, which emits rays of several tens of million volt energy, should be helpful in cancer therapy. High and low energy roentgen rays differ not only with regard to depth dose distribution. Consideration of physics and radiation biology lead us to expect additional differences of medical importance, differences that concern elements of cell size and do not depend on the dosage distribution over a large area. Theoretically, the reaction of any such small volume element to high energy roentgen rays should compare with the reaction resulting from about an equal dose of Ra-γ-rays. Several experiments were designed to study the comparative biological effects of high and low energy roentgen rays with elimination of all differences in depth dose distribution. The results thus far obtained confirm the expectations.

It will be feasible in the near future to utilize the betatron in cancer therapy. It must be emphasized that

this will not result in any radical change in the outlook of cancer patients, but we can confidently expect a modest improvement both in the number of cures and in the way in which treatments are administered and tolerated. A project to utilize the betatron for therapy with fast electrons is being pursued. Such a development would open interesting fields in clinical and fundamental research.

THE EFFECT OF STILBESTROL ON ADVANCED CANCER OF THE BREAST. IRA T. NATHANSON. (Medical Laboratories of the Collis P. Huntington Memorial Hospital of Harvard University, Tumor Clinic of the Massachusetts General Hospital, and Pondville Hospital, Boston, Mass.)

A number of carcinogenic hydrocarbons possess the property of retarding the growth of normal and malignant tissue. Estrogens are similar in chemical structure to some of the carcinogens. This prompted a group of English investigators to treat advanced cancer with certain estrogens. Accordingly we treated a series of women with advanced cancer of the breast with relatively large doses of stilbestrol. Preliminary observations indicate that stilbestrol may exert an initial beneficial although apparently temporary effect on the primary tumor in a number of patients. In this group ulcerations decreased in size or became epithelialized, masses became smaller, skin changes appeared and cicatrization was observed. The effect on the metastases is still open to question. In general, the favorable responses were confined to older women. Usually the disease in younger women was unaltered in its course or was possibly accelerated. This phenomenon is of interest since it is one of the few examples in which a malignant tumor is influenced by an administered humoral agent. The mechanism of action is not clear.

THE LIPIDS AND LIPID-RICH TUMORS OF THE TESTIS. CHARLES HUGGINS, PAUL RUSSELL and P. V. MOULDER. (Department of Surgery, University of Chicago, Chicago 37, Ill.)

The lipids of the testis of normal dogs vary over a limited range; they are distributed in the cells of Leydig and Sertoli. Tumors arising from these cells are rich in fat; tumors of the interstitial cells produce masculinization while the sustentacular cell tumors often produce feminization. These tumors constitute a further example of neoplasms of physiologic maturity. Neither estrogen nor hypophysectomy abolish the testicular lipids although the function of these cells is reduced and prostatic atrophy results therefrom.

HISTOGENESIS OF MOUSE MAMMARY CANCER INDUCED WITH METHYLCHOLANTHRENE. ARTHUR KIRSCHBAUM, W. LANE WILLIAMS, and JOHN J. BITTNER. (University of Minnesota Medical School, Minneapolis 14, Minn.)

When methylcholanthrene dissolved in benzene was painted on the skins of forced-bred, female mice of certain genetic types, they developed grossly visible, multiple nodules in the mammary gland. Forced breeding alone did not induce this type of nodule formation. These nodules are considered to be carcinogenically-induced, and they developed in either the presence or the absence of the milk agent. Although in whole mount preparations, as viewed under low magnification, the nodules resembled the "hyperplastic nodules," which precede "milk-agent tumors," sections of the carcinogen-induced nodules revealed a decidedly different histology. The nodules developed as a result of injury to the epithelium of the ducts and proximal alveoli by the carcinogen, followed by a proliferative squamous epithelial response. These alterations were succeeded by neoplasia. The frank cancers that developed from carcinogen-induced nodules were of mixed squamous and alveolar structure. Susceptibility to the carcinogenic induction of mammary cancer is not common to all strains, and this susceptibility cannot be correlated with susceptibility to spontaneous mammary cancer. The histological evidence does not favor the concept that the carcinogen accelerates the sequence of alterations seen in the histogenesis of spontaneous "milk-agent tumors" of mice.

SOME EXPERIMENTAL RESULTS OBTAINED DURING THE WAR IN THE LABORATOIRE PASTEUR DE L'INSTITUT DU RADIUM DE PARIS. RAYMOND LATARJET.

In new-born and adult mice, methylcholanthrene has been applied to cutaneous fields that had previously been subjected to either ultraviolet irradiation with a well-defined high dosage, or to the removal of a cutaneous disc. The scars, free from hair follicles and sebaceous glands, always appeared refractory to the carcinogenic action of the hydrocarbon. On the other hand, the skin zones in which repair after photodermatitis had occurred under conditions such that some hair follicles with sebaceous glands had been restored or were newly formed, gave rise to rapidly evolving epitheliomas. In both cases, the proliferating strips surrounding the scar and underlying the process of repair displayed a high sensitivity to the carcinogenic action of the hydrocarbon.

Three rabbits were exposed to well-defined doses of neutrons produced by the beryllium target of a cyclotron. Two of them developed a visceral cancer, which was almost certainly caused by neutrons.

More than 20 new compounds have been prepared by fixation of several methyl groups on the nucleus of 5,6-benzacridine and 7,8-benzacridine. While the 5,6-compounds were nearly inactive, their 7,8-isomers frequently displayed a more or less strong carcinogenic activity. (10 compounds of 14 biologically tested). Some of them showed a power close to that of methylcholanthrene, giving about the same latency and the same percentage of tumors. The 3,10-dimethyl-7,8-benzacridine seemed even more carcinogenic than the 20-methylcholanthrene.

It has been shown that the addition of a weakly carcinogenic hydrocarbon to a highly carcinogenic similar compound reduces the activity of the latter. The following samples have been tested in this way:

Methylcholanthrene + dibenzofluorene
" + di-methyl 5,6-benzacridine
" + dimethyl 7,8- ....
1,2,5,6-dibenzanthracene + 1,2,5,6-dibenzacridine

Such antagonisms seem to involve a process of competition between the two chemicals.

The milk "influence" has been observed varying with the strain of mice. It appeared very seldom in one in which the mammary glands reacted weakly to the experimental stimulation by estrogen. This influence has been indirectly transmitted by injection of mammary gland extracts to the offspring, but it did not seem to "multiply" in tissue cultures.

Extensive theoretical studies have been performed along the line opened by Otto Schmidt and followed by Swartholm, on the relation between carcinogenic power and the electronic distribution in the molecule. Laws have been determined for the calculation of mesomeric figures in aromatic hydrocarbons, and these figures have been studied for several hundreds of these compounds. According to wave mechanics, the distribution of the π electrons (electrons of the double bonds) has been determined and the sites of high electronic density located. These sites fit usually with the points of high chemical reactivity. In most of the carcinogenic hydrocarbons actually known there exists a special *"région aromatique activée" or "région méso-phénanthrènique"* which consists of a double bond highly charged (1 to 1,5 e) between two atoms highly charged (0.75 to 1 e).

CARCINOGENESIS AND CELL ADAPTATIONS. R. R. SPENCER. (National Cancer Institute, Bethesda 14, Md.)

During the past 5 years studies have been made of the action of carcinogenic agents upon free-living single-cell species based upon the theory that the process we call carcinogenesis and the process by which such organisms become adapted to unfavorable environments may have certain features in common. Essentially 3 concepts are involved in this theory:

1. That the cancer process is, in part at least, a *special type* of cellular adaptation to various unusual environments. Not all cell adaptations end in cancer. Reptiles and amphibians rarely respond to carcinogenic agents. Woolley, Fekete and Little have shown that cancer of the adrenal cortex may be induced by removal of the ovaries and testicles of new born mice of the Ce strain but not in other inbred strains.

2. That the transformation of a normal cell to a cancer cell involves a step-like process. There is no clinical or experimental evidence to support the assumption that the genesis of a cancer cell involves a sudden change in a normal cell. On the other hand, the clinically observed association of cancer with chronic irritation; the various pre-cancerous lesions and stages; the prolonged incubation period in all experimentally induced cancers; and such fundamental observations as Earle's *in vivo* transformation of a single clump of normal cells to cancers of 6 or 7 different types of behavior, all seem to fit in with the concept of *gradualism* in the genesis of cancer.

3. That the cancer process is basically a survival mechanism. It has been pointed out that the universal goal of living things is survival, but the survival of the cancer cell is a thing apart from that of the organism as a whole.

Our studies have yielded results that have suggested that there are several important principles involved in the mechanism by which species become adapted to unfavorable environment.

Experimental data were presented by means of lantern slides supporting the following tentative principles:

1. The *continuous* exposure of actively multiplying free-living, bacterial species to an unfavorable environment may not be fatal to individual organisms or cultures for a number of generations or cell-division cycles, but in due time the species will die.

2. By discontinuous or alternating exposure, an actively multiplying species can adapt and continue to survive in an environment that is fatal when the exposure is continuous.

3. The ability of an organism to resist an unfavorable environment is a function of its age or maturity.

4. Organisms can resist higher intensities of an unfavorable environment during the resting stage than during the actively multiplying stage.

The belief was expressed that a continuation of these studies will lead to a better understanding of the underlying principles and mechanisms concerned in species adaptation.

SUSCEPTIBILITY OF MICE TO LEUKEMOGENIC AGENTS. HARRY W. MIXTER and ARTHUR KIRSCHBAUM. (Department of Anatomy, University of Minnesota, Minneapolis 14, Minn.)

Mice of the Bagg A, Strong A, C3H, C57, NH, CBA, and dba-subline 212 strains were exposed to x-rays in varying doses. X-rays were leukemogenic for all of these strains.

Leukemia rarely occurs spontaneously in any of these stocks, with the exception of strain dba-subline 212, in which the incidence is 25 per cent.

Of these stocks only the dba was susceptible to the induction of leukemia with methylcholanthrene. Under the same method of application of the carcinogen (skin-painting 3 times weekly with a 0.25 per cent solution in benzene) the other strains were completely refractory. Mice of the C3H and Bagg A stocks exhibited definite but not pronounced susceptibility to the induction of leukemia with estrogens.

Susceptibility to the induction of leukemia with x-rays was observed in the 7 strains tested, whereas only 1 demonstrated susceptibility to either spontaneous leukemia or the carcinogenic induction of the disease. The data indicate that strain specific susceptibility might exist for some, but not for other leukemogenic agents.

INCREASE IN INCIDENCE OF PULMONARY TUMORS IN STRAIN A MICE FOLLOWING LONG-CONTINUED IRRADIATION WITH γ-RAYS. EGON LORENZ, WALTER E. HESTON, MARGARET DERINGER, and ALLEN B. ESHENBRENNER. (National Cancer Institute, Bethesda 14, Md.)

Sixty strain A mice (35 males and 25 females) were exposed daily for 8 hours to γ radiation from a 1 gm. radium source filtered by 0.5 mm. platinum; the daily

dose was $8.8 \pm 10\%$ r γ. The same number of control mice were kept. The animals were from 1 to 2 months old at the beginning of the experiment. Exposure was terminated after 287 days when the experimental animals had received a total dose of $2{,}500 \pm 10$ per cent r γ. The incidence of lung tumors in the experimental animals was 77 per cent and in the control animals 47 per cent. This difference is statistically significant.

THE INFLUENCE OF A REST PERIOD ON THE CARCINOGENICITY OF ULTRAVIOLET IRRADIATION APPLIED IN INTERRUPTED DOSES. H. P. RUSCH and B. E. KLINE. (McArdle Memorial Laboratory, Medical School, University of Wisconsin, Madison 6, Wis.)

To determine the influence of varying periods of rest on the response to the carcinogenic action of ultraviolet irradiation applied in interrupted doses, several groups of albino mice were subjected to an initial dose of ultraviolet light and then given rest periods before the application of a second subcarcinogenic dose. The dosage was the same for all groups, 468×10^7 ergs per cm.^{2} The mice were rayed daily for 6 days a week, and except for the control groups the total dose was applied in two periods that were interrupted by varying periods of rest. In most groups the initial dose was applied for 3 months, an amount previously shown to induce only a low incidence of ear tumors with the conditions used. Periods of from 1 to 3 months were allowed before the mice were re-rayed for another 2 months. Eight months after the beginning of the experiment, the final tumor count was recorded as follows: an incidence of 83, 50, and 29 per cent was observed in three groups that had been allowed 1, 2, or 3 months' rest between the first and second raying periods respectively. The number of tumors found in a control group, which had obtained uninterrupted radiation was 87 per cent. It appears, therefore, that two periods of subcarcinogenic doses of ultraviolet irradiation have the same effectiveness as a similar total dose of continuous application of these rays, provided that the period of rest does not exceed 1 month. However, when the length of the rest period is greater than one month, an indirect proportion between the duration of the rest period and the incidence of neoplasms is observed.

SUCCINIC DEHYDROGENASE AND CYTOCHROME OXIDASE IN EPIDERMAL CARCINOGENESIS IN MICE INDUCED BY METHYLCHOLANTHRENE. C. CARRUTHERS and V. SUNTZEFF. (Barnard Free Skin and Cancer Hospital, St. Louis 3, Mo.)

Previous investigations from this laboratory have shown that the calcium, iron, copper, and zinc contents of methylcholanthrene-treated (hyperplastic) mouse epidermis were much lower than normal untreated and benzene-treated epidermis, and also that the content of these metals was still lower in a transplantable squamous cell carcinoma, originally derived from mouse skin by the application of methylcholanthrene. Therefore, assays of succinic dehydrogenase, because of its possible relationship to calcium, and cytochrome oxidase, because of a possible association with copper and/or iron, were carried out. Samples of the various treated epidermises were homogenized and assayed for the enzymes by Potter's methods. The QO_2 values for succinic dehydrogenase and cytochrome oxidase of the epidermis of normal untreated controls, and of the epidermis of benzene-treated mice (3 and 6 applications of benzene on alternate days, and the mice sacrificed 5 days after the last treatment) did not differ significantly. Likewise the epidermis of mice that had received 3 and 6 applications of a 0.6 per cent solution of methylcholanthrene in benzene on alternate days and sacrificed 5 days after the last treatment did not show any appreciable change in the QO_2 value for these enzymes. The enzymes are now being assayed in late hyperplasias and in the squamous cell carcinoma.

UPTAKE OF P_{32} IN THE PHOSPHOLIPID FRACTION OF MOUSE EPIDERMIS UNDERGOING CARCINOGENESIS BY METHYLCHOLANTHRENE. C. J. COSTELLO, C. CARRUTHERS, and M. KAMEN. (Barnard Free Skin and Cancer Hospital and Department of Radiology, Washington University Medical School, St. Louis, Mo.)

Normal untreated epidermis, benzene-treated epidermis and methylcholanthrene-treated (hyperplastic) epidermis were removed from the dermis at 50° C., and the phospholipids were extracted by refluxing with a mixture of 3 parts of alcohol and 1 part of chloroform. Each sample was extracted twice with the solvent mixture, and the latter evaporated to dryness on a steam bath. The residue remaining was then re-extracted with petroleum ether which was evaporated on a steam bath. The phospholipid was then oxidized to orthophosphate by digestion with nitric and perchloric acids. The orthophosphate was determined colorimetrically by the method of Truog and Meyer. The fat-free epidermis was dried at 105° C. and used as a basis of reference, and the results were expressed as milligrams of phospholipid per 100 mgm. of dry, fat-free epidermis. This ratio for normal and benzene-treated epidermis was nearly 4.0, and for hyperplastic epidermis about 3.0, a decrease of 25 per cent. On the other hand the ratio had almost doubled for the transplantable squamous cell carcinoma. Our first studies on the uptake of P_{32} using exactly the same method of extraction and digestion show no difference between normal and benzene-treated epidermis. Results on the hyperplastic epidermis and on the carcinoma will be completed shortly.

VITAMIN CONTENT OF MOUSE EPIDERMIS DURING METHYLCHOLANTHRENE CARCINOGENESIS. E. L. TATUM, MARY RITCHEY, E. V. COWDRY, and L. F. WICKS. (Department of Biology, Stanford University, Calif., Department of Anatomy, Washington University and Barnard Free Skin and Cancer Hospital, St. Louis, Mo.)

The levels in biotin, choline, inositol, *p*-aminobenzoic acid and pyridoxine content of mouse epidermis have been followed during methylcholanthrene carcinogenesis by the use of mutant strains of *Neurospora*. No significant

changes in inositol, choline, or *p*-aminobenzoic acid were observed and the pyridoxine content appeared to increase slightly after treatment with either methylcholanthrene or with benzene. The biotin content was found to decrease only with methylcholanthrene treatment, reaching a level of 64 per cent of normal after a single application of the carcinogen, and maintaining approximately the same value with repeated paintings over a period of 60 days.

THE EFFECT OF LIVER EXTRACT, EGG ALBUMIN, CYSTINE, AND CYSTEINE UPON *p*-DIMETHYLAMINOAZOBENZENE CARCINOGENESIS IN RATS. PAUL N. HARRIS, M. E. KRAHL, and G. H. A. CLOWES. (Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Ind.)

Although addition of 3 per cent of "Liver Extract, Lilly" to a rice-carrot diet resulted in striking retardation of carcinogenesis, addition at the level of 15 per cent gave appreciably less protection. This effect was presumably due to biotin, since the addition of biotin at the level in the 15 per cent liver diet to a 3 per cent liver diet resulted in a tumor incidence like that of the 15 per cent liver diet. Addition of 3 per cent of "Liver Extract, Lilly" to a diet containing 20 per cent casein and 5 gamma of riboflavin per gram did not retard tumor development. A diet containing 15 per cent of egg albumin and 3.9 gamma of riboflavin per gram offered striking protection against tumor development, even as compared with a diet containing 20 per cent casein and 8 gamma of riboflavin per gram. Cystine and cysteine offered pronounced protection against carcinogenesis when added at the level of 1 per cent to diets containing 20 per cent of casein and 5 to 8 gamma of riboflavin per gram, but with diets low in casein and riboflavin the effect was less impressive. Folic acid at the level of 0.2 gamma per gram of diet afforded no protection against carcinogenesis, although the mortality rate on this diet was lower than that on the control diet.

EFFECT OF DRIED SPLEEN UPON THE PRODUCTION OF LIVER MALIGNANCIES IN RATS BY *p*-DIMETHYLAMINOAZOBENZENE. ANNA GOLDFEDER. (New York City Cancer Institute and the Laboratories of Cellular Physiology, New York University, New York, N. Y.)

The production of liver tumors in rats fed a diet containing *p*-dimethylaminoazobenzene is now a well established fact. The addition of various preparations to the diet containing the carcinogen such as: liver, kidneys, beef, as well as yeast, vitamins, oils and other substances caused an inhibitory effect to a greater or lesser extent in the development of malignant growths in the livers of rats, as reported by various investigators. A few data are available on the effect of the spleen on liver carcinogenesis by *p*-dimethylaminoazobenzene.

The spleen has special significance in cancer research. It has proved to be one of the potent organs in inducing a resistant state in animals to transplanted tumors, particularly in hybrids. It is one of the organs of the reticuloendothelial system, the latter being directly involved in immunological processes. It was of interest, therefore, to investigate the effect of the spleen in liver carcinogenesis on a wider basis.

The purpose of this communication is to report the observations made from two groups of rats of Sherman stock: *Group A,* regarded as controls, was fed a diet consisting of the same ingredients as used by previous investigators, *i.e.,* of coarsely ground unpolished rice to which 0.06 per cent of *p*-dimethylaminoazobenzene dissolved in cottonseed oil was added. This diet was supplemented with a slice of fresh carrot and water daily. *Group B* were rats who received the same diet but in addition 10 per cent of dried spleen was added.

Up to date (January 15, 1946) 236 days elapsed since the start of the experiments. While all of the control rats (group A) developed tumors of the liver within a period of 64 to 170 days and are dead by now, only 8 per cent of group B, receiving dried spleen in addition to the carcinogen, showed malignant changes in the livers at a much later date and to a lesser extent. The majority of these rats are still alive and appear normal.

It may be concluded that dried spleen added to the diet containing *p*-dimethylaminoazobenzene has an inhibitory effect on liver carcinogenesis.

THE CARCINOGENICITY OF 1,2,3,4-DIBENZOPHENANTHRENE AND ITS 9-METHYL AND 10-METHYL DERIVATIVES IN MICE. PAUL N. HARRIS and CHARLES K. BRADSHER. (Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Ind., and Department of Chemistry, Duke University, Durham, N. C.)

The hydrocarbons were suspended in tricapryllin or the ethyl ester of sesame oil and injected subcutaneously into New Buffalo mice. The dose of the 9-methyl derivative was large and variable; 850 mgm. were divided among 32 mice. The usual dose of the other two compounds was 5 mgm. Twenty-six mice received the parent compound; 1 developed an epidermoid carcinoma at the site of injection, 3 developed both epidermoid carcinoma and sarcoma, and 15 developed sarcoma. The latent period ranged from 10 to 42 weeks and averaged 19 weeks. Ulcers developed at the site of inoculation in 14 mice, and in 10 of these, tumors appeared later. The 4 carcinomas occurred in this group. Neither tumors nor ulcers developed in mice that received the 9-methyl or 10-methyl derivatives.

ON THE FAILURE OF DIETARY MODIFICATION TO INFLUENCE CARCINOGENESIS BY 2-ACETYLAMINOFLUORENE IN RATS. PAUL N. HARRIS. (Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Ind.)

Three diets were used: (1) a 20 per cent casein-high riboflavin diet, (2) a 13 per cent casein-low riboflavin diet, and (3) the second diet with the addition of 3 per cent of "Liver Extract, Lilly." The carcinogen was incorporated in the diet at a level of 0.4 mgm. per gm., and administration was never discontinued.

With *p*-dimethylaminoazobenzene as the carcinogen,

the use of these or of very similar diets produced conspicuous effects upon the development of hepatic tumors; diet (2) caused fairly rapid tumor development; diet (1) appreciably retarded tumor growth and diet (3) produced striking protection against tumor development. When the carcinogen 2-acetylaminofluorene was used, there was no significant difference in hepatic tumor development in rats receiving these 3 diets.

Differences in appearance of the livers and liver tumors of rats receiving the two carcinogens were described, and the other tumors produced by 2-acetylaminofluorene were discussed briefly.

Present Status of a Joint Institutional Research Program on Chemotherapy of Cancer.

I. CURRENT LABORATORY AND CLINICAL PROJECTS WITH BACTERIAL POLYSACCHARIDE, SYNTHETIC COMPOUNDS, AND OTHER MATERIALS. M. J. SHEAR. (National Cancer Institute, Bethesda 14, Md.)

Previous investigators have reported that certain materials are capable, under restricted conditions, of damaging or killing tumor cells, but none of these materials has been considered to be of practical value when given parenterally. Among these agents are: bacterial culture filtrates; colchicine; sodium cacodylate; auramine; and acriflavine. These earlier experiments have been repeated in our own laboratories and the findings of others have been confirmed with respect both to the effects of these materials on tumors in experimental animals and to the apparent limitations of some of them as therapeutic agents.

Instead of discarding these materials as disappointing, we have considered them as encouraging leads and are attempting to find out how far the clues will take us in the direction of developing some agent of greater value. With the aid of various working hypotheses, related materials have been selected, prepared, or synthesized, on a substantial scale. These substances have been put through various processes to screen out those that possess desirable properties accompanied by a minimum of undesirable properties. On the basis of correlations found between chemical structure and toxicity to the host, and between chemical structure and activity in damaging tumor cells in mice, new materials have been designed with the objective of developing substances of greater potency combined with lowered toxicity. In addition, the nature of the drawbacks encountered in the employment of some of these agents has been studied, and attempts are being made to avoid or overcome them.

These systematic, integrated studies are being conducted by mature specialists in various fields, *e.g.*, organic chemistry, bacteriology, cytology, histopathology, physiology, etc., together with the clinical specialists. The independent investigators have associated themselves voluntarily in this co-ordinated program. The organizations represented at the present time are: the National Cancer Institute, and the Laboratory of Zoology, of the National Institute of Health, Bethesda; the Lankenau Hospital Research Institute and the Institute for Cancer Research, Philadelphia; the Department of Physiology of the Hahnemann Medical College, Philadelphia; and the Cancer Research Division of the Donner Foundation.

II. NECROSIS PRODUCED IN TRANSPLANTED MOUSE CARCINOMAS WITH *S. MARCESCENS* POLYSACCHARIDE. THELMA B. DUNN and STEPHANIE LEHMANN. (National Cancer Institute, Bethesda 14, Md.)

Bacterial polysaccharide was given intraperitoneally to mice bearing various types of transplanted epithelial tumors. On gross examination 24 hours after a single injection of 0.1 milligram, the tumors appeared unchanged. Microscopic examination, however, showed extensive necrosis of tumor tissue, although a few remaining tumor cells could still be found in nearly every section. The types of epithelial tumor in which this effect has been noted are a squamous cell carcinoma derived from the forestomach; an adenocarcinoma derived from the small intestine; a myoepithelioma of the salivary gland; a pulmonary tumor; and a recently transformed spindle cell tumor, which originally grew as a squamous cell carcinoma of the skin. It appears, therefore, that the effect of the bacterial polysaccharide is not limited to sarcomas, and that the effect on carcinomas may be overlooked unless microscopic examinations are made.

III. CYTOLOGICAL EFFECTS OF *S. MARCESCENS* POLYSACCHARIDE ON TUMORS. IRENE COREY DILLER and M. J. SHEAR. (Lankenau Hospital Research Institute, and Institute for Cancer Research, Philadelphia, Pa., and National Cancer Institute, Bethesda 14, Md.)

A study has been made of the cytological effects produced in tumors with a polysaccharide isolated by Shear and co-workers from culture filtrates of *S. marcescens* (*B. prodigiosus*). As previously reported, intraperitoneal injection of this material into tumor-bearing mice is followed within a few hours by production of macroscopic hemorrhage in the tumors and by necrosis of tumor tissue. Primary sarcomas as well as transplanted sarcomas responded to this agent in the same way.

The microscopic studies reveal equally striking degenerative changes and, particularly, damage to cell nuclei. A single intraperitoneal injection of 0.01 mgm. of the polysaccharide into a mouse bearing sarcoma 37 produces microscopic changes in the tumor, which are observable as early as 2 hours after treatment. The initial response is a dissociation of the tissue into discrete cell entities, accompanied by a swelling of the nucleus and blistering of the nuclear membrane. Nuclei thus affected pass through a process of progressive shrinkage, and reach a maximum of degenerative change at about 6 hours after injection of the bacterial metabolite. The terminal effect is manifested by total disruption of the nucleus, accompanied by attenuation of the nuclear substance, which at times involves extrusion into the cytoplasm of individual chromosomes drawn out into extremely long, thin filaments.

There is evidence that cells which are most affected are those which were in some stage of division at the

time of impact of the polysaccharide. At four hours after injection, no division is detected, and when undamaged cells persist after six hours they are in resting stage. Rapidly dividing normal tissues (of which the most susceptible material studied thus far is intestinal epithelium of the mouse) are also damaged similarly by the polysaccharide.

In addition to transplanted tumors, several spontaneous neoplasms of rats and of mice have been studied, as well as biopsy and post-operative material from sarcomas of patients treated with the polysaccharide. The nature of the nuclear response is similar in all material studied, though it varies in degree and extent. In a significant proportion of the mice bearing sarcoma 37, cell damage following treatment with this agent was irreparable, and led to complete destruction of the tumors.

IV. GROSS AND MICROSCOPIC PATHOLOGY OF HUMAN TUMORS FOLLOWING ADMINISTRATION OF *S. MARCESCENS* POLYSACCHARIDE. S. P. REIMANN, A. L. HOLLOMAN, R. OAKEY, JANE R. McCONNELL, and M. J. SHEAR. (Lankenau Hospital Research Institute and Institute for Cancer Research, Philadelphia, Pa., and Hospital Division and National Cancer Institute, U. S. Public Health Service.)

Without previous sensitization, injection of a polysaccharide prepared from *B. prodigiosus* (*S. marcescens*) produces necrosis and hemorrhage in both animal and human tumors. Injections were intravenous or intraperitoneal in single or divided doses, or by constant intravenous drip in a few patients. In about half the patients, pain appeared in the tumor area within a few hours after the injection accompanied by swelling of the tumor region. In a day or two, if the tumor was near the surface, diffuse light ecchymosis appeared. The amount of necrosis and hemorrhage varied, apparently determined by the size of the tumor; in patients, the larger the tumor the more scattered, and the smaller the tumor, the more obvious the necrosis and hemorrhage. In one recurrent melanosarcoma, about the size of an English walnut, the hemorrhage was enough to allow a spurt of blood on sectioning of the tumor. Workers on other aspects of this program have found that production of necrosis with this agent is not contingent upon prior production of hemorrhage.

Microscopically the necrosis is a liquefaction type, with hemorrhages in the necrotic areas, at times focal and at times larger. The explanation of the focal necrosis, with hemorrhage in the area, is supplied by the findings of others that it is particularly cells in division which are acted upon by the polysaccharide.

Since the softer sarcomas are notoriously subject to hemorrhage, distinction between hemorrhage from polysaccharide and from other causes is sometimes a fine one Since, however, fibrosarcomas show the least, and often practically no hemorrhage, the presence of necrosis and hemorrhage in these tumors is of more significance. The cellular studies in all cases bear out the pathological topographical interpretations.

V. EFFECT OF *S. MARCESCENS* POLYSACCHARIDE ON RECTAL TEMPERATURES IN NORMAL AND IN TUMOR-BEARING MICE. LYLE V. BECK and MARY FISHER. (Department of Physiology, Hahnemann Medical College, Philadelphia 2, Pa.)

Tumor-bearing patients develop high fever when treated with a polysaccharide from *S. marcescens*. In our own experiments measurable fever was produced in the normal rabbit by 0.005 µgm. per kgm. of the polysaccharide injected intravenously, and a high fever by 0.5 µgm. per kgm. Fever was also produced by bigger doses, the largest amount tested being 100 µgm. per kgm. A search of the literature failed to unearth data about any other purified substance having anything like as great a pyrogenic action in the rabbit as this polysaccharide.

Experiments on mice indicate that there is no necessary relation between the pyrogenic action of the polysaccharide and its tumor-necrotizing action. Shear and his coworkers (J. Nat. Cancer Inst., **4**:99-105. 1943) have found that the amount of polysaccharide capable of producing some hemorrhage and necrosis in mouse sarcoma 37 in half the mice tested is 0.1 µgm. intraperitoneally. In the present experiments the polysaccharide was given to both normal and tumor-bearing mice intravenously in amounts ranging from 0.01 to 10 µgm. (about 0.4 to 400 µgm. per kgm.), and intraperitoneally in amounts ranging from 0.5 to 10 µgm. Of approximately 2,000 rectal temperature readings made on about 300 mice no pyrogenic response was recorded; in fact the larger amounts of polysaccharide produced decreases in rectal temperature, which were more pronounced and longer lasting in tumor-bearing than in normal mice. Also the larger the tumor the greater was the temperature drop, and the smaller the chance of survival.

VI. SELECTION AND SYNTHESIS OF ORGANIC COMPOUNDS. J. L. HARTWELL, M. J. SHEAR, J. M. JOHNSON, and SYLVIA R. L. KORNBERG. (National Cancer Institute, Bethesda 14, Md.)

Compounds to be used in testing for action against tumors in mice were selected as follows: (a) substances reported in the literature to have an injurious effect on dividing normal cells, on tumors, or on tumor cells, (b) substances reported to have activity against amebae, trypanosomes or other microörganisms, and (c) compounds related chemically to those mentioned above.

Among the substances in the first group were colchicine, narcotine, certain α,β-diphenylethylamines, acriflavine, suramine, and the arsenic derivative sodium cacodylate. Of these, only narcotine was inactive. Notably active among the diphenylethylamines were α,β-diphenylethylamine and α-(3,4-methylenedioxyphenyl)-β-phenylethylamine.

Among the compounds of the second group were emetine, chiniofon, rivanol, germanin, atabrine, quinine, a few representatives each of the classes of amidines, arsenicals, antimonials, and "sulfa" compounds. Of these, emetine, rivanol, germanin, atabrine, stilbamidine, neoarsphenamine, sulfarsphenamine, and fuadin were active.

The compounds of the third class constitute the largest number of those to be tested. Many series of these have been synthesized by us, or obtained from other sources. Among the series about which considerable information has been obtained are four (A, B, C, and D) represented by the partial formulas—(Note: Structural formulae were shown. The diagrams have been omitted from this abstract. Ed.) Series B and D are so far the most interesting in respect to both percentage of active members and their potency. Some compounds in each of these groups exhibiting activity are as follows: (A) suramine, dichlorodiphenyltrichloroethane (DDT), *p,p'*-dimethoxybenzophenone; (B) the two α,β-diphenylethylamines mentioned earlier, and stilbamidine; (C) 1-(4-phenoxyphenyl)-2, 3-dipiperidino-3-phenylpropanone-1 and 1,3-di-(4-methoxyphenyl)-2,3-dimorpholinopropanone-1; and (D) 1-phenacyl-2-picolinium iodide, 1-(2-naphthacyl)-pyridinium iodide oxime, and 1-(β-phenethyl)-pyridinium bromide.

There are at present more than 800 selected compounds in our continually growing collection, which are being screened to reveal the small percentage of active ones. The screening process will be described in the following paper.

VII. FIRST SCREENING IN TUMOR-BEARING MICE: SEGREGATION OF ACTIVE FROM INACTIVE COMPOUNDS.

VIRGINIA PETERS, J. L. HARTWELL, A. J. DALTON, and M. J. SHEAR, (National Cancer Institute, Bethesda 14, Md.)

To segregate compounds active in damaging tumor cells, hybrid mice bearing intramuscular implants of sarcoma 37 were used. The maximum tolerated dose, previously determined for non-tumor-bearing hybrids, was injected subcutaneously. At autopsy 8, 20, and 48 hours later, samples of tumors and intestines were fixed for histologic and cytologic study, and the gross appearance of the tumors was noted. Based on microscopic findings, 200 compounds, of the 800 on hand, have been classified according to the presence or absence of activity in damaging tumor cells. It was found that there was no necessary correlation between lethality and activity.

In addition to those reported in the preceding abstract, the following compounds yielded microscopic evidence of severe damage to the tumors: cephaeline hydrochloride; corydine hydrochloride; 1-(*p*-methoxyphenacyl)-3-picolinium iodide; 1-(*p*-methoxyphenacyl)-4-picolinium iodide; 2-phenacylisoquinolinium iodide; proflavine; and *d*-tubocurarine chloride.

In another category were 40 other compounds that damaged tumor cells sufficiently to warrant examination of further substances with structures related to them.

VIII. CYTOPATHOLOGICAL CHANGES IN SARCOMA 37 PRODUCED WITH A SINGLE SUBCUTANEOUS INJECTION OF ORGANIC COMPOUNDS.

A. J. DALTON and VIRGINIA PETERS. (National Cancer Institute, Bethesda 14, Md.)

In resorting to histologic and cytologic studies to screen out the inactive compounds we have made the assumption that damage induced by active compounds would become evident within 48 hours after injection. It has been found possible to distinguish histologically and cytologically between the so-called "spontaneous necrosis" and damage induced by the injection of active compounds. The type of induced damage is not specific but is considered a characteristic cellular reaction associated with the physical and chemical changes involved in rapid cell death. The changes are mainly in the nucleus. Chromatin becomes concentrated immediately beneath the nuclear membrane where it segregates into small droplets with light-staining centers and dark-staining margins. The small droplets coalesce into larger ones. With eventual disintegration of the nuclear membrane and the cytoplasm, the deeply staining chromatin droplets remain for some time as free individual particles. Similar changes are sometimes seen in areas of spontaneous necrosis but as a rule the two types of damage may be readily distinguished partly because nuclear degeneration in "spontaneous necrosis" usually follows a different path and partly because cells exhibiting induced damage are all in more or less the same stage of change.

Damage to normal host intestine by active compounds has varied from severe, with extensive sloughing of epithelium, to relatively mild, with the appearance of granular acidophilic cytoplasm and slight condensation of chromatin in epithelial cells at the tips of villi.

IX. SECOND SCREENING IN TUMOR-BEARING MICE: FURTHER POTENCY AND TOXICITY EXPERIMENTS WITH THE ACTIVE COMPOUNDS.

M. J. SHEAR, VERONICA ARMAGHAN, A. J. DALTON, and J. L. HARTWELL. (National Cancer Institute, Bethesda 14, Md.)

The compounds found in the first screening to possess potency in damaging or killing cells of sarcoma 37 following subcutaneous injection of a single sublethal dose, were subjected to further experimentation. The approximate value for the maximum tolerated dose in a single injection, obtained in the first screening, was determined more precisely for each compound in 32 tumor-bearing mice divided into 4 groups of 8 mice each. Another batch of 56 mice bearing week-old implants of sarcoma 37 was then divided into 7 groups of 8 mice each, and single injection of the maximum tolerated dose was given to 40 of them. These were sacrificed, one group at a time, after 8, 24, 40, 56, and 72 hours. Of the 16 controls, one group was killed with the first group of test mice, and one with the last group. Gross observations were made, smears of tumor cells prepared according to the acetic-orcin technic were observed microscopically as well as tumor tissue prepared according to routine histologic methods and stained with hematoxylin and eosin. From this type of experiment the time of maximum tumor damage was ascertained.

The minimum effective dose was then determined on a batch of mice, bearing week-old sarcoma 37, divided into groups of 8 each. One group served as a control;

each of the other groups received a single subcutaneous injection of a given compound in a progressively decreasing dose. All mice were sacrificed at the time of maximum damage as described previously. Material from the tumor was examined microscopically to ascertain the minimum dose which produced damage to the cells.

Illustrative experiments were given. Attempts to produce regression of tumors are being deferred until data on the effects of repeated injections upon tumors and upon normal tissues are obtained with those compounds found to possess high activity combined with low toxicity.

THE VASCULAR REACTION OF NORMAL AND NEOPLASTIC TISSUES TO A BACTERIAL POLYSACCHARIDE FROM *BACILLUS PRODIGIOSUS* CULTURE FILTRATE. GLENN H. ALGIRE. (National Cancer Institute, Bethesda 14, Md.)

Photographs and daily quantitative measurements were made of the vascular bed in the normal (striated muscle) and neoplastic (transplanted sarcoma) tissues included within a transparent chamber introduced into a dorsal skin flap in the mouse, prior to and following intraperitoneal injection of the polysaccharide.

In the development of the reaction there occurred a decrease in the capillary supply to the panniculus carnosus layer of striated muscle and to transplanted sarcomas. This quantitative decrease in functional capillaries was accompanied by stasis and occlusion. Capillary dilatation was not observed.

In the capillaries of the striated muscle layer the vascular occlusion reached a maximum in from 3 to 4 hours, and in the animals that survived, recovery of capillary function occurred within 18 hours. Neither hemorrhage nor necrosis was observed in these normal tissues.

The progressive development of capillary occlusion in transplanted sarcomas was followed, at the end of 3 to 4 hours, by petechial hemorrhages throughout the tumor. In spite of the apparently complete necrosis that developed, a few tumor cells survived, which retained the capacity to elicit a new vascular supply, and growth was resumed.

THE DISSOCIATION OF PROTAMINE-NUCLEATES BY AROMATIC DIAMIDINES. M. J. KOPAC. (Department of Biology, Washington Square College of Arts and Sciences, New York University, New York, N. Y.)

These investigations were made possible by the development of micro-surface-chemical methods. The dissociation of protamine-nucleate complexes was estimated by measuring the adsorption of liberated protamine at appropriate oil-water interfaces. At 0.001 to 0.002 *M*, stilbamidine diisethionate produced an appreciable denaturation of protamine molecules. Stilbamidine at similar concentrations dissociated protamine-nucleate complexes to release partially denatured protamine molecules and, simultaneously, trapped the nucleate by the formation of insoluble stilbamidine-nucleate complexes. Propamidine diisethionate, on the other hand, did not dissociate protamine-nucleate complexes nor did it produce any significant denaturation of the protamine molecules. Propamidine, however, formed relatively insoluble complexes with free nucleic acids. Thus, by surface chemical means, one property of stilbamidine diisethionate, not shared by propamidine diisethionate, has been demonstrated; *e. g.*, protamine-nucleate dissociation. This may account for the differences shown by the action of these compounds on living cells (with collaboration of Gladys Cameron and Robert Chambers). Stilbamidine selectively destroyed certain types of neoplastic cells, in tissue culture; *e. g.*, mammary adenocarcinoma R2426 (rat) and transplantable lymphosarcoma (rat). With propamidine, both normal and neoplastic cells either survived or were destroyed depending on the concentration. This compound is, therefore, non-specific in its action on neoplastic cells.

Phenamidine and pentamidine were also non-selective in their action on neoplastic cells. Furthermore, none of the diamidines except stilbamidine enhanced significantly the surface denaturation of serum albumin molecules.

Other compounds structurally similar to stilbamidine are being synthesized. If these new derivatives can dissociate model nucleoprotein systems, as shown here, then such compounds should also destroy selectively certain types of neoplastic cells. Studies with stilbamidine and related compounds have indicated that one approach to tumor-chemotherapy is by way of selective nucleoprotein dissociation. The protamine-nucleates used in these investigations were crude models of the many highly specialized nucleoproteins that may be found in living cells. Similar measurements on other nucleoproteins, *e. g.*, liver, virus, and mitochondrial nucleoprotein complexes, are in progress.

PREVENTION OF ADRENAL CORTICAL CARCINOMA BY DIMETHYLSTILBESTROL. GEORGE W. WOOLLEY and C. C. LITTLE. (Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Me.)

We have observed that adrenal cortical carcinomas, normally expected in JAX strain ce mice when gonadectomized soon after birth, did not appear following treatment of such mice with an estrogenic substance, diethylstilbestrol. Fusion pellets, 25 per cent diethylstilbestrol in cholesterol, av. wt. 4.8 mgm. were used. Although the effectiveness of diethylstilbestrol as a substitute for natural gonadal secretion in preventing adrenal cortical tumor formation is clear, further study is needed to find a protective agent for tumors of the adrenal cortex that will not at the same time cause other serious body disturbances. In the present experiment pituitary tumors of the type caused by estrogenic hormones were observed in diethylstilbestrol-treated mice as early as 7 months of age. The relation of these pituitary tumors to the inhibitory action of diethylstilbestrol on the adrenal cortex depends for its solution upon further investigation now being planned.

DEVELOPMENT OF LEIOMYOMATA IN FEMALE RATS WITH AN ENDOCRINE IMBALANCE. CARROLL A. PFEIFFER. (Department of Anatomy, Yale University School of Medicine, New Haven 11, Conn.)

Uterine tumors are extremely rare in rats. Pyometra

is usually produced by the chronic injection of estrogens, and if tumors of the uterus occurred one would expect them to be fibromas. It was thought that in female rats that have an endocrine imbalance because of the presence of a testis graft during the prepubertal period, the continuous existence of the endogenous estrogen might cause the uterus to become susceptible to the development of leiomyomas. However, even here the constant estrous condition allows the development of pyometra which is usually severe enough to cause death of the animals eventually. Of 171 of these females that had received testis grafts into the neck region at birth only 12 survived for more than 3 years. These were autopsied and leiomyomas were found in 3 of them. One animal had pyometra but whether this condition has any relation to the formation of the leiomyomas is not known. All of the animals probably had suffered from pyometra at one time or another. The tumors ranged from 1 to 3 cm. in greatest diameter; all were composed only of smooth muscle cells. Although the tumors displaced both the serosa and the endometrium, they did not invade them.

MAMMARY TUMOR INCIDENCE AND OCCURRENCE OF GROWTHS OF THYROID TISSUE IN THE LUNGS OF MICE AFTER PROLONGED INGESTION OF THIOUREA AND THIOURACIL. HAROLD P. MORRIS, CELIA S. DUBNIK, and ALBERT J. DALTON. (National Cancer Institute, Bethesda 14, Md.)

The effects of prolonged ingestion of thiourea and thiouracil in diets of natural foodstuffs have been studied in virgin female C3H mice. Adult animals started when approximately eleven months of age on 0.375 per cent thiourea showed a slight decrease in body weight and no appreciable decrease in food intake. The feeding of 0.375 to 0.5 per cent thiouracil starting with young mice resulted in animals of lower body weight compared with the untreated controls, and a somewhat lower food intake. Twenty of 21 animals receiving thiourea and 20 of 23 controls developed mammary carcinomas. The average time after the start of the experiment until the development of tumors was 16.2 weeks for the treated and 8.8 weeks for the controls. Ingestion of thiouracil, however, starting when the mice were one and a half months of age definitely reduced the incidence of mammary tumors. At 18 months 94 per cent of 52 untreated and only 17 per cent of fifty-two treated animals had mammary tumors.

There was observed in the treated animals a distinct atrophy of the ovaries and uterus and a decreased weight of the adrenal. The mammary duct system was underdeveloped or atrophied. Prolonged periods of anestrous were common. The thyroid gland showed the expected hypertrophy. This gland in the treated group attained weights 5 to 20 times those of the controls. On October 3, 1945, after 11 months of thiouracil ingestion an animal which died was found at autopsy to have numerous small, greyish, raised nodules on the lung surfaces. These were found to be thyroid tissue on histologic examination. Since that time a total of 9 out of 29 lungs examined were found to contain metastatic nodules of thyroid tissue.

The data suggest that these two goitrogenic substances may not only inhibit normal thyroid secretions, but may indirectly affect mammary carcinogenesis in mice by inducing atrophy of some other endocrine glands, and inhibiting their secretions, especially those which promote the growth and development of the mammary gland. Accompanying the inhibition of normal thyroid secretion, however, there occurs a tremendous hypertrophy of this gland, which in the case of thiouracil, after prolonged ingestion may eventually result in metastases of thyroid tissue to the lungs.

THYROID CHANGES INDUCED BY PROLONGED FEEDING OF THIOUREA. AUBREY GORBMAN. (Department of Anatomy, Yale University School of Medicine, New Haven 11, Conn.)

Study has been made of the thyroid gland in mice fed a diet containing 2 per cent thiourea for periods varying from 7 to 541 days. Mice of two inbred strains, A and C57, F_1 hybrids of the A×C3H and C57×CBA strains, and "BC" mice obtained by backcrossing PM×C3H hybrids with the C3H stock, were used in this work.

Initial hypertrophy of the follicular epithelium was followed by follicular and papillary hyperplasia. After 200 or more days of treatment formation of follicular cysts, as much as 1 mm. in diameter, was common, especially in the cortex of the gland. The cysts underwent complex papillary and follicular filling, which sometimes obliterated their lumina. Secondary follicles usually formed within cysts, and within these, sometimes, tertiary follicles.

Remarkable increases in vascularity were observed in the gross as well as microscopically. Large venous sinuses formed within the gland, and into these many follicles projected, separated only by endothelium. Degenerative changes, confined to the thyroid and resembling thrombi, were noted in the walls of veins and some arteries.

The relation of thyroid epithelium to blood sinuses in stimulated glands, and the discovery in two instances of thyroid-like cells in veins, prompted an examination of lung for possible transported thyroid cells. In several instances small islands of thyroid-like cells, showing high mitotic activity, were found in the lung. This finding must be interpreted with caution because resumption of a normal diet in long-treated mice leads to involution of the activated epithelium.

THE INFLUENCE OF SEX HORMONES UPON THE HEPATIC LESIONS PRODUCED BY 2-ACETAMINOFLUORENE. A. CANTAROW, K. E. PASCHKIS, J. STASNEY, and M. S. ROTHENBERG. (Jefferson Medical College, Philadelphia, Pa.)

The observation that the simultaneous administration of 2-acetaminofluorene, a carcinogen, and the antithyroid drug, allylthiourea, leads to the development of tumors of the thyroid, suggested that it would be interesting to investigate the influence in this connection of other agents that stimulate growth of specific tissues.

Two hundred and fourteen rats (Sherman) were divided

into six experimental groups. All received 2-acetaminofluorene in their food. One group served as controls, the others receiving in addition to the carcinogen one of the following substances: alpha-estradiol dipropionate, testosterone propionate, PMS gonadotropin, chorionic gonadotropin, and thiouracil. Animals were sacrificed after 5½ to 7 months of treatment.

The most striking findings were in the livers of animals receiving estradiol or testosterone, or gonadotropins that stimulated increased production of gonadal hormones. The livers showed advanced stages of nodular hyperplasia and cystic cholangioma, which were either absent or of mild degree in those receiving thiouracil or the carcinogen alone. These lesions have been described previously in rats receiving the carcinogen for longer periods.

It appears that excessive quantities of intrinsic or extrinsic estrogenic and androgenic steroids hasten and intensify hepatic lesions induced by acetaminofluorene. This is of particular interest because of the role the liver plays in the metabolism and excretion of steroid hormones.

ACTIVITY OF THE MAMMARY TUMOR MILK AGENT AS INFLUENCED BY AGE AND HORMONAL STIMULATION IN SERIAL DILUTION STUDIES. JOHN J. BITTNER. (Department of Physiology, Division of Cancer Biology, University of Minnesota Medical School, Minneapolis 14, Minn.)

Extracts of either lactating mammary glands from mice with the milk agent or spontaneous mammary tumors may give, when injected into mice of comparable ages, higher incidences of mammary tumors when diluted 10^{-3} or 10^{-4}, than 10^{-1}. A few tumors have resulted following the injection of a dilution of 10^{-6}. The incidences are influenced also by the age of the animals at the time of treatment. The inhibitory effects in both the host and the injected material may be partially overcome by subjecting the inoculated animals to increased hormonal stimulation.

THE INCIDENCE OF MAMMARY TUMORS AND THE STRUCTURE OF MAMMARY GLANDS OF ESTROGEN PLUS TESTOSTERONE-TREATED MICE. W. U. GARDNER. (Department of Anatomy, Yale University School of Medicine, New Haven 11, Conn.)

Several investigators have observed an incidence of mammary tumors subsequent to treatment with testosterone in female mice of tumor-susceptible strains. The reduced incidence might be attributable to the reduced ovarian function of such animals. Few studies have been made in which extrinsic estrogens were added to compensate for ovarian deficiency coincident with prolonged androgen treatment.

To determine whether testosterone propionate might have a specific inhibitory effect on mammary proliferation or a mammary tumor inhibiting effect mice of the high tumor C3H strain were used. Seventy-three per cent (133 of 183) of the breeding females of this strain acquired mammary cancer at a mean age of 339 days; 39 per cent of 111 virgin female mice had mammary tumors at a mean age of 492 days.

Among 118 estrogen-treated mice (97♂, 21♀) 51 died with mammary cancer at a mean age of 325 days. The estrogen was injected subcutaneously in doses ranging from 3.3 to 33.3 µgm. of estradiol benzoate weekly. Among 180 mice (88♂, 92♀) given comparable doses of estrogen and 0.625 to 2.5 µgm. of testosterone weekly, 17 had mammary cancer (average 424 days). The larger doses of testosterone were relatively more effective than the smaller. The mammary glands of the mice treated with estrogen and androgen contained few localized nodules and consisted primarily of large ducts. The usual growth-stimulating effects of estrogen were partially inhibited in the male mice that had been given estrogens. Testosterone inhibited both the normal mammary proliferation and precancerous proliferation, as demonstrated by the few hyperplastic nodules, and the low incidence of cancer.

THE EFFECT OF DIETARY PSEUDO-HYPOPHYSECTOMY UPON THE DEVELOPMENT OF THE MAMMARY GLANDS AND MAMMARY TUMORS IN MICE RECEIVING DIETHYLSTILBESTROL. ZELDA B. BALL, R. A. HUSEBY, and M. B. VISSCHER. (Department of Physiology, Division of Cancer Biology, University of Minnesota Medical School, Minneapolis 14, Minn.)

To determine the extent to which diethylstilbesterol administered orally would stimulate mammary growth in mice whose pituitary function has been decreased by caloric restriction, weanling A strain females were placed on a diet restricting their caloric intake approximately one-third that consumed by the fully fed controls. Diethylstilbesterol was added to the food of both groups so that all animals ingested the same amount of the drug each day, the dose being twice that found to produce continuous vaginal cornification. Histological study of the mammae after 15 months of this regimen revealed that the glands of the restricted animals were considerably less developed than were those of the control mice and also less than those of normal virgin mice of the A strain. Thus, further evidence that the degree of pituitary function is reflected in the development of the mammary glands was obtained even though relatively high levels of estrogenic stimulation are maintained exogenously. The dietary pseudo-hypophysectomy was further reflected in the incidence of mammary carcinoma, for, although no tumors have occurred in the restricted group, mammary tumors have developed in 25 per cent of the control mice with 22 per cent of these animals still living.

RELATIONSHIP OF THE INHERITED SUSCEPTIBILITY AND THE INHERITED HORMONAL INFLUENCE IN THE DEVELOPMENT OF MAMMARY CANCER IN MICE. JOHN J. BITTNER and ROBERT A. HUSEBY. (Department of Physiology, Division of Cancer Biology, University of Minnesota Medical School, Minneapolis 14, Minn.)

Observations obtained on breeding females of the cancerous A and Z (C3H) stocks and their reciprocal F_1 and F_2 hybrids were in accord with the theory that the mice of these two strains may have the same inherited susceptibility for mammary cancer.

The difference in the incidence of mammary cancer in the virgin females of the A and Z stocks was due to gene action in controlling some hormonal mechanism. This effect has been called the inherited hormonal influence and probably results from the action of multiple genes. Inherited susceptibility and the inherited hormonal influence are probably not produced by the same genes.

The characteristics (concentration and/or activity) of the milk agent may differ in mice of the A and Z stocks and influence the incidences of mammary tumors that were observed in the virgin hybrids. The differences were not apparent in the breeding hybrids with increased hormonal stimulation.

Each inciting influence in the genesis of mammary cancer in mice may be almost completely determining in its effects, and thus be of equal importance.

CASTRATION EFFECTS ON THE INHERITED HORMONAL INFLUENCE. FERN W. SMITH. (Department of Physiology, Division of Cancer Biology, University of Minnesota Medical School, Minneapolis 14, Minn.)

Female mice of the high cancerous A and C3H stocks and two groups of their reciprocal hybrids, one with and one without the milk agent, were castrated at the time of weaning and were observed for evidences of adrenal hyperplasia and of estrogenic stimulation.

Those mice having the inherited hormonal influence, as the C3H and their hybrids, developed adrenal cortical hyperplasia, and later in life many were found to have adrenal cortical tumors. That these adrenal abnormalities produced estrogenic substances was evidenced by vaginal cornification, uterine growth, and extensive mammary gland development. Mammary tumors appeared frequently in these animals when the milk agent was present but not in its absence. In the mice of the A strain, which lacked the inherited hormonal influence, neither gross nor histological changes of the adrenals were noted. None of these animals exhibited cornification of the vaginal epithelium or uterine hypertrophy.

THE GENETIC CONTROL OF OVARIAN SECRETION AS RELATED TO THE INCIDENCE OF MAMMARY CANCER IN MICE. ROBERT A. HUSEBY, FERN W. SMITH, and JOHN J. BITTNER. (Department of Physiology, Division of Cancer Biology, University of Minnesota Medical School, Minneapolis 14, Minn.)

In an attempt to characterize the genetically determined, physiological mechanisms involved in the production of mammary tumors in virgin mice, F_1 hybrid mice between the A and Z (C3H) strains were spayed and transplanted with ovaries of the parent stocks and of other F_1 hybrid mice. In this manner the variables involved were reduced to those resident in the ovaries of the donor animals as these would be subjected to the same pituitary stimulation and the hormones produced by these ovaries would be acting upon the same end-organ substrate and be metabolized in the same manner. Vaginal smear data collected during the first ten months of the experiment revealed no statistically significant differences in the amount of cornification or the degree of variability of the estrous cycles in the three groups of hybrid mice bearing these different ovarian grafts, although the degree of variation encountered was somewhat greater than that found in normal mice of the F_1 hybrid stock. The incidence of tumors in the hybrid animals with Z and with hybrid ovaries was, nevertheless, significantly higher than in those bearing A strain ovaries. These latter data are interpreted as indicating that the secretions of the Z and F_1 hybrid ovaries are more "carcinogenic" than are those of the A strain ovaries when all other factors are, as nearly as can be determined, equal.

THE INCIDENCE OF MAMMARY TUMORS IN CASTRATE AND NON-CASTRATE MALE MICE FOLLOWING OVARIAN TRANSPLANTATION. ROBERT A. HUSEBY, FERN W. SMITH, and JOHN J. BITTNER. (Department of Physiology, Division of Cancer Biology, University of Minnesota Medical School, Minneapolis 14, Minn.)

Young F_1 hybrid males of the $A \times Z$ cross were transplanted with ovaries of similar F_1 hybrid females, and about half of the male animals were castrated, Whereas only one (2.5 per cent) of the un-castrated group developed a mammary tumor, 84 per cent of the castrated animals have been so afflicted. The average age at which the castrated males developed tumors was 11.3 months or 6 months younger than virgin females of this stock. Histological examination of the mammae revealed that, although the glands of the castrated group were extensively developed, those of the un-castrated animals showed no more development than seen in normal male mice of this stock, in spite of the fact that the ovarian grafts were well maintained as judged by histological appearance. Evidence to indicate that these ovarian grafts were functional was obtained by transplanting uterine fragments into similar animals. In those males bearing ovarian transplants whether castrated or un-castrated, these uterine transplants became cystic and the epithelium showed signs of stimulation while similar grafts in intact male mice were retained but did not become cystic, nor did the epithelium show histological evidence of stimulation.

THE SULFHYDRYL GROUPS OF RAT LYMPHOSARCOMA CATHEPSIN. MARY E. MAVER and J. W. THOMPSON. (National Cancer Institute, Bethesda 14, Md.)

The specific role of the protein sulfhydryl groups in the activity of many different enzymes has been investigated by Bersin, Hellerman, Chinard and Dietz, and Barron and Singer. Evidence is presented here that the activity of the endocellular proteinase, or cathepsin, separated from rat lymphosarcoma is dependent upon protein sulfhydryl groups. The proteinase activity was inhibited progressively with increasing amounts of iodine, sodium iodosobenzoate, *p*-chloromercuribenzoate and 3-amino-4-hydroxyphenyldichlorarsine hydrochloride. The enzymes inhibited by the latter two reagents could be reactivated under certain conditions by treatment with excess glutathione. The total

sulfhydryl groups of the lymphosarcoma cathepsins were titrated with sodium iodosobenzoate and ferricyanide after denaturation with guanidine hydrochloride. The results are of particular interest in a study of the effects of oxidation reduction conditions upon the proteolytic enzymes of neoplastic tissues.

ACTIVITY OF PROTEOLYTIC ENZYMES IN *p*-DIMETHYLAMINOAZOBENZENE-INDUCED HEPATOMAS. PAUL C. ZAMECNIK and MARY L. STEPHENSON. (Medical Laboratories of the Collis P. Huntington Memorial Hospital of Harvard University, at the Massachusetts General Hospital, Boston, Mass.)

A comparison of the activity of catheptic enzymes at pH 5 and of peptidase activity at pH 8 has been made in hepatomas induced in rats by *p*-dimethylaminoazobenzene and in the livers of controls. Rats were killed at various intervals on the diet and the enzymatic activity of their livers was determined, using the synthetic peptide substrates of Bergmann. No remarkable change in these enzymes was found until hepatomas had developed. The activity of the catheptic proteinase responsible for the hydrolysis of benzoyl-*l*-argininamide was consistently increased in the hepatomas, as compared with the various control livers—"prehepatomas," regenerating, fetal, and normal adult. The other proteolytic enzymes for which tests were made either showed no significant changes in the hepatoma or, as in one case, (substrate leucylglycine, pH 8) showed a decrease in activity detectable after the development of the hepatoma.

ENZYMATIC ACTIVITY IN PRIMARY AND TRANSPLANTED RAT HEPATOMAS. JESSE P. GREENSTEIN. (National Cancer Institute, Bethesda 14, Md.)

When normal liver becomes neoplastic certain components alter in magnitude (Category I) while others remain unaffected (Category II). Category I includes arginase, catalase, alkaline phosphatase, cystine desulfurase, dehydropeptidase II, succinic oxidase, cytochrome oxidase, cytochrome *c*, riboflavin, esterase, transaminase, glyoxalase, histidase, and the systems concerned with urea synthesis. Category II includes acid phosphatase, the nucleodesaminases, dehydropeptidase I, adenosinetriphosphatase, overall dehydrogenase systems, the nucleases, phosphorylase, benzoylarginineamidase, and creatine and creatinine.

On transplantation of the primary hepatoma, certain of the components in Category I alter in magnitude (Category III) while others do not change (Category IV). Category III includes arginase, catalase, alkaline phosphatase, dehydropeptidase II, and the urea-synthesizing mechanisms. Furthermore, as a result of transplantation, certain of the components in Category II alter in magnitude (Category V), while others do not change (Category VI). Category V includes acid phosphatase, the nucleodesaminases, the overall dehydrogenase systems, and benzoylarginineamidase.

Changes in the catalytic components of the livers of tumor-bearing rats occur in a direction which the liver would take if it became neoplastic. Thus, those systems, which alter from normal in the livers of tumor-bearing rats, are found only in those of Category I and not in Category II. The tumor borne by these animals need not be a hepatoma to elicit this effect. The fact that certain components of the liver alter in a direction which would be taken if the liver became neoplastic suggests that the presence of a distant tumor may be reflected in a greater or less degree of "cancerousness" in susceptible tissues elsewhere in the host.

RHODANESE AND THE PASTEUR EFFECT. B. MENDEL, H. RUDNEY, and M. C. BOWMAN. (Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada.)

Rat tissues that display a high anaerobic glycolysis may be divided into two groups: (a) tissues such as brain, testes, spleen, and ileal mucosa, in which the glycolysis is suppressed in O_2 almost to the maximum anticipated from the Meyerhof quotient; (b) tissues, such as malignant tumors (S39, Jensen sarcoma), retina, kidney medulla and jejunal mucosa, in which the glycolysis in O_2 is not reduced to the extent which could be expected from the magnitude of the respiration. It has been found that tissues belonging to group (a) contain large amounts of rhodanese whereas in those of group (b) this enzyme, if present at all, is found in insignificant amounts. Rhodanese catalyzes the formation of thiocyanate from HCN and S-containing compounds and could thus detoxify any HCN produced in metabolism.

It is known that small amounts of thiocyanate are excreted at a constant rate in the urine and, though the mechanism of the formation of this compound is unknown, it could conceivably originate in the interaction of HCN and S-containing substances—the reaction catalyzed by rhodanese. Since concentrations of HCN smaller than those that interfere with the oxygen uptake have been shown to offset the effect of O_2 on glycolysis, it is suggested that, in tissues exhibiting aerobic glycolysis, the accumulation of HCN that would occur in the absence of rhodanese could account for the partial or total abolition of the Pasteur effect.

DETERMINATION OF CODEHYDROGENASE I IN TUMORS. F. SCHLENK. (University of Texas, M. D. Anderson Hospital for Cancer Research, Houston, Texas.)

Determinations of codehydrogenase I (diphosphopyridine nucleotide) in tumor tissues were carried out using the apozymase test. Particular care was exercised with respect to the reference standard of codehydrogenase and the method of extraction. Freezing of tissue samples in dry ice for transportation and crushing in the frozen state was found satisfactory. As soon as the cellular structure is destroyed, rapid enzymatic splitting of the coenzyme is observed. The codehydrogenase I content of a variety of animal and human tumor tissues was found to be low. Extraction with dilute acid and dilute alkali made it possible to determine the ratio: coenzyme/dihydrocoenzyme. In most tissues the oxidized form is in excess, while in some tumors the reduced coenzyme is predomi-

nant. Attempts to correlate the excess of reduced coenzyme with the amount of reducing specific substrate have failed.

NUCLEIC ACIDS IN HUMAN TUMORS. ROBERT E. STOWELL. (Department of Pathology, Washington University School of Medicine, St. Louis 10, Mo.)

The relative content of nucleic acid per unit volume of tissue and per cell was measured by photometric histochemical methods in 20 human tumors. The thymonucleic acid was determined by measuring the relative absorption of light in tissues stained by the Feulgen reaction. The ribose nucleic acid was estimated by determining photometrically the decrease in pyronine staining produced by the action of ribonuclease enzyme. The nucleic acid content of tumors and corresponding normal cells were compared with mean measurements of cell volume, cytoplasm, nucleus, nucleolus, chromatin, and nuclear sap. As compared with homologous normal tissues, the thymonucleic acid content per unit volume of tissue was significantly increased in 11 tumors, slightly increased in 7 and slightly decreased in 2. Thymonucleic acid per cell was increased significantly in 9 tumors, slightly in 9 and decreased slightly in 2. Of the 9 tumors in which ribose nucleic acid was estimated, it was materially increased per volume in 4, slightly in 2 and slightly decreased in 3. The amounts per cell were increased greatly in 4, slightly in 3 and decreased slightly in 2. The content of thymonucleic acid per unit volume was highest in tissues with small cells and with a low proportion of cytoplasm. The amounts of thymonucleic acid per unit volume and per cell showed considerable variation in relation to the proportion of nuclear and chromatin material.

THE EFFECT OF NITROGEN MUSTARDS ON NUCLEIC ACID: VISCOSITY AND SPECTROPHOTOMETRIC MEASUREMENTS. ALFRED CHANUTIN and ERLAND C. GJESSING. (Biochemical Laboratory, University of Virginia, Charlottesville, Va.)

It is known that the nitrogen mustards (beta-choroethyl amines) undergo successive transformation in aqueous solution. The rate of transformation differs for each agent. The first of these products is an active intermediate ethylenimonium ion. The toxic effects of the nitrogen mustards apparently are due not to the compounds themselves, but to the reactive intermediates. It is known that sodium thiosulfate reacts with the imine ring to produce a non-toxic compound.

The effect of 3 nitrogen mustards I, ethyl-bis (chloroethyl) amine; II, methyl-bis (chloroethyl) amine and III, tris (chloroethyl) amine, on the viscosity of thymonucleic acid solutions was determined. Immediately after mixing III with nucleic acid, a significant decrease in viscosity was noted while compounds I and II had little effect. This difference was due apparently to the rates of formation of transformation products. However if the nitrogen mustards (I and II) were allowed to react in an alkaline solution until the first imine rings were formed, the viscosity of the nucleic acid was decreased significantly. It was found that the greater the concentration of the agent, the more pronounced was the effect on viscosity. Comparatively small amounts of these agents are necessary to produce this effect. An amount of sodium thiosulfate calculated to react with the potential imine rings was added to a mixture of compound III and nucleic acid solution. This nitrogen mustard no longer affected viscosity. This is considered to be evidence that sodium thiosulfate removed the active imine. The ultraviolet absorption spectra were determined before and after mixing tris (chloroethyl) amine with thymonucleic acid solutions, uracil, xanthine, adenine and guanine. Relatively large amounts of the agent were necessary to produce a shift in the absorption spectrum of nucleic acid to longer wave lengths. This shift became more pronounced with increasing amounts of the agent. Similar shifts in the spectrum were noted after the treatment of uracil and the 3 purines. These changes probably represent the formation of new compounds.

ISOLATION AND CHARACTERIZATION OF PROTEOSE FROM HUMAN PLASMA. RICHARD J. WINZLER, ARTHUR W. DEVOR, and JOHN W. MEHL. (Department of Biochemistry, University of Southern California Medical School, Los Angeles, Calif.)

With a view toward evaluating the significance of the elevated blood proteose levels found in patients with cancer, a study of the chemistry of proteose isolated from normal human blood has been undertaken. Proteose was prepared from pooled normal human plasma after precipitating the proteins with perchloric acid, dialysis of the filtrate to remove low molecular weight constituents, and salting out the proteose with ammonium sulfate. Electrophoretic analysis of one such sample showed three fractions separable at pH 8.5. The major component, comprising 70 per cent of the total, had a mobility of 13.2×10^{-5} cm^2/sec./volt. The other two components had mobilities of 12×10^{-5} cm^2/sec./volt and 10×10^{-5} cm^2/sec./volt. It was possible to isolate the slowest component free from the first two by fractionation with ammonium sulfate. The nitrogen contents of a mixture of the three components as well as of the separated third component alone were the same at 9.3 per cent. This is in accord with previous results on rat blood proteose. The sulfur content of samples prepared from perchloric acid and from sulfosalicylic acid filtrates of plasma were 0.5 and 0.7 per cent respectively, in striking contrast to the very high values obtained previously with rat blood proteose.

The presence in normal plasma of these three clearly distinguishable proteose components as well as very small amounts of a peptone-like component not salted out by ammonium sulfate raises the question of how the proportions of the four components may be altered as a result of the increase in total blood proteose observed in the blood of patients with cancer.

PARENTERAL THIAMIN TOLERANCE IN CANCEROUS INDIVIDUALS. RIGBY C. ROSKELLEY, L. MURIEL SCHLEGEL, and WILLIAM T. SAL-

TER. (Laboratories of Pharmacology and Toxicology, Yale University School of Medicine, New Haven 11, Conn.)

When the thiamin tolerance of cancerous human patients is tested by oral administration of the vitamin, they tend to show a diminished ability to store *free* thiamin. When a similar test is performed by parenteral administration of thiamin this feature disappears, as judged by non-cancerous controls. The peak of the urinary excretion is reached sooner than in the oral test, and both cancerous and noncancerous patients respond similarly. When PAYF excretions are compared, the cancerous subjects show no significant difference from the noncancerous.

Why does the parenteral tolerance test in cancerous patients fail to disclose the tendency toward relative thiamin deficiency found by the oral test? Destruction of the vitamin within the gut or failure of absorption by the intestine seem not to be adequate explanations of the difference between the enteral and parenteral effects. A tentative explanation is advanced that, when injected, free thiamin is present in such excess that the quantitative ability of tissues to metabolize it is obscured.

INTERRELATIONSHIPS BETWEEN BIOTIN, CARBON DIOXIDE, AND HEAVY METALS (CO, CU) IN TUMOR GLYCOLYSIS, FERMENTATION, AND DEHYDROGENATION.

DEAN BURK, MARIE L. HESSELBACH, CLARA FISCHER, JOHN HEARON, and ARTHUR L. SCHADE. (National Cancer Institute, Bethesda 14, Md., and Overly Biochemical Research Foundation, New York 21, N. Y.)

Addition of avidin (ca. 10 units (2 mgm.)/cc.) to stationary, cell-free, nucleus-free, sand-ground, aerated, 1:10 aqueous or 0.01*M* phosphate, approximately neutral extracts of mouse (or rat) liver initially equilibrated with air and methylene blue (4 p.p.m.), increased the rate of reduction of the methylene blue and equilibrated oxygen slightly in the presence of endogenous substrate and much more so in the presence of added lactate, ethyl alcohol, pyruvate plus bicarbonate, or oxaloacetate, all of which are known to reduce oxidized coenzymes I and II. The increase in reduction rate caused by avidin with any of these substances was decreased in varying degree by biotin (ca. 30 p.p.m.), and equally well by O-heterobiotin (ethyl alcohol and lactate tested). With succinate (for the oxidation of which no known coenzyme is required), avidin decreased the reduction rate, and in a manner not reversed by biotin. None of the effects of avidin described were obtained with like quantities of concentrates of egg albumin, egg globulins (including crystalline lyzozyme) or conalbumin, and only much less effectively with a variety of avidin preparations of lower potency, including egg white itself. It is provisionally concluded from these experiments that biotin accelerates (and avidin inhibits) a reduction reaction requiring hydrogen or electrons derived apparently non-specifically from any of various substrates that act through the mediation of reduced coenzyme I or II (or oxidation-reduction system components in further equilibrium therewith; *e.g.,* reduced flavoprotein). It is evident that biotin plays a profound role in liver metabolism, and is potentially capable of producing local, systemic, precancerous, and procarcinogenic effects, some of which may be reversed by avidin and, presumably, by other anti-biotins more closely related to biotin in structure.

Cobalt inhibited the growth of spontaneous mammary adenocarcinomas in mice and of many aerobic and anaerobic, pathogenic and non-pathogenic microorganisms (*e.g.,* Clostridia, streptococci, staphylococci, colon bacteria, yeast), and also secondarily the respiration (though scarcely fermentation or glycolysis) of these materials and of a variety of animal tissues, somewhat higher concentrations of Co and longer exposure times being required with respiration than with growth. The concentration functions ranged from 1 to 100 p.p.m. Co (added as, *e.g.,* $CoCl_2$), depending upon the cell concentration, type of medium, exposure time, etc. Under proper conditions, complete inhibition of growth of proteus could be obtained with zero inhibition of respiration. Co inhibiton of both growth and respiration was overcome specifically by histidine added at a mnimum of two molecules of histidine per atom of Co, and less effectively by cysteine (with which a different, sulfhydryl linkage is effected), and not appreciably by other amino acids tested, histamine, or adenylic acid. Tolerance doses of Co by mice could be raised many fold by the concurrent injection of histidine at dosages only several fold greater than molecularly equivalent.

The locus of cobalt action in growth has not been identified beyond possible combination with histidine, cysteine (sulfhydryl), or amino acids such as alanine, with which an oxygenated complex is likewise formed, slowly in comparison to the 2 histidine: 1 cobalt complex, which forms immediately upon mixing in air, as is readily evident visually or spectroscopically. Respiration inhibition has been found to be correlated with an inhibition of the succinate dehydrogenase system, experiments with oxidation of amino acids, pyruvate, and malic acid by resting proteus cells and transaminase action having proved negative. Reduction of methylene blue and O_2 in the presence of added succinate, by various bacteria (*e.g., E. coli, M. lysodeikticus*) and mouse liver, heart, and breast adenocarcinoma, was inhibited by Co over the same concentration range as was respiration, as was likewise reduction by Na_2S (but not by ascorbic acid). The Co might thus inactivate by combining with the sulfhydryl groups in the succinic dehydrogenase enzyme protein itself, but Co^{++} has also been observed, in *in vitro* experiments carried out with Dr. B. L. Horecker, to combine rapidly with oxidized cytochrome *c,* in the presence of a substance, such as cyanide, with which Co forms a complex with considerably more positive oxidation-reduction potential. Co may, therefore, unfavorably lower the ratio of oxidized to reduced cytochrome *c,* and even of oxidized to reduced cytochrome oxidase, and so inhibit utilization of mobilized substrate hydrogen. This action would be much the same as that of paraphenylenediamine, except that paraphenylenediamine is in addition a substrate itself, whose oxidation ordinarily increases the observed overall oxygen consumption, more so in normal than in tumor

tissues; likewise Co causes a smaller inhibition of respiration in normal than in tumor tissues; generally. The action of Co in the succinate dehydrogenation is largely duplicated by copper at somewhat lower concentrations, and the latter is likewise inhibited by histidine, by forming a complex therewith, evident visually and spectroscopically.

FACTORS AFFECTING THE CYTOCIDAL ACTION OF X-RAYS *IN VITRO*. ROBERT SCHREK. (Tumor Research Unit, Hines Veterans Hospital, Hines, Ill.)

The 50 per cent survival time of cells in radiated (1,000 r) and non-irradiated suspensions was determined by the method of unstained cell counts and an empirical index of radiosensitivity was calculated. The factors studied were:

(a) *Type of cells.*—High indices of radiosensitivity were obtained for thymic and splenic cells of the rabbit (74 and 62) and for the blood cells of normal men (32) and of three lymphatic leukemic patients (86 to 73); low indices, for the cells of rabbit bone marrow (7) and of human myelogenous leukemic blood (11).

(b) *Species of animals.*—Radiated and non-radiated thymic cells of the kitten had longer 50 per cent survival periods (16.5 and 39.0 hours) than those of the rabbit (5.2 and 20.0 hours). The indices of radiosensitivity were only slightly different (74 and 58).

(c) *Temperature.*—Non-irradiated thymic cells survived longer when incubated at lower temperatures than at higher, with a temperature coefficient of approximately 3. Cells radiated at 25° C. had a maximum index of radiosensitivity when incubated at 37° (74) and a minimum at 17° and 45° C. (3 and 0). Cells irradiated at 0° and 25° C. and incubated at 37° C. had the same radiosensitivity (74 and 68).

(d) *Acids and alkalies.*—Addition of moderate amounts of NaOH or NH_4OH had no definite effect on the survival of radiated cells. Moderate amounts of lactic, acetic, and hydrochloric acids added after radiation inhibited the cytocidal action of X-rays; the radiated cells survived as long as the non-radiated.

EFFECTS OF RADIOACTIVE SODIUM ON LEUKEMIA IN MICE. TITUS C. EVANS. (Radiological Research Laboratory, College of Physicians and Surgeons, Columbia University, New York 32, N. Y.)

Effects of radioactive sodium and whole body roentgen irradiation on white mice (Swiss strain) have been compared. Equivalents of the two types of radiation have been obtained for effect on the blood counts and survival. Mice of the Ak strain with various forms of lymphadenopathy have been given subcutaneous injections of radioactive sodium. Animals with enlarged nodes and extremely high leukocyte counts were found especially sensitive to the radio-sodium. There was no significant increase in the concentration of radiosodium in leukemic nodes over that of the blood. The marked response of the leukemic cells was therefore related to their greater radiosensitivity. It was possible to reduce the leukocyte count (without reducing number of erythrocytes) for longer periods by fractionation than by single massive dosages.

THE POSSIBLE ASSOCIATION BETWEEN PORPHYRINS AND CANCER IN MICE. JOHN J. BITTNER and CECIL JAMES WATSON. (Departments of Physiology, Division of Cancer Biology, and of Medicine, University of Minnesota Medical School, Minneapolis 14, Minn.)

The values obtained by extraction of porphyrins from the harderian glands of virgin and breeding females of various inbred stocks of mice and the F_1 hybrids provided data on the possible association between porphyrins and cancer in mice. There is no apparent decrease in the porphyrin content of the harderian glands with the increasing age of the animals. No relationship could be found between the presence of the active milk agent and the porphyrins. There is no simple correlation between the inherited susceptibility for mammary and lung cancer and the porphyrins. In every stock the breeding females showed higher porphyrin concentrations in the harderian glands than did the virgin females. Spayed females may show higher readings than virgin females. The maximal concentrations of porphyrins in the various groups were attained at different ages. The apparent relationship between the porphyrins and mammary cancer, as described by others, may be due to a correlation of unknown nature between the porphyrins and the hormones. In virgin females this association may involve the inherited hormonal influence.

THE LUMINESCENCE-PORPHYRIN PHOTOSENSITIZATION THEORY OF CARCINOGENESIS. FRANK H. J. FIGGE. (University of Maryland School of Medicine, Baltimore 1, Md.)

Carcinogenesis involves the complete photo denaturation of specific nucleoproteins that normally assist in regulating cell division. The denaturation results from the direct action of ultraviolet light (2,900 to 3,300 A.) and indirect action of shorter and longer wave lengths of light. The shorter radiations excite molecules in or near the nucleus to luminesce or emit carcinogenic ultraviolet light (2,900 to 3,300 A.). Longer wave lengths of light (3,400 to 4,500 A.) denature or assist in the denaturation of nucleoproteins when specific photosensitizing substances (prophyrins) are present.

Carcinogenic chemicals fall into one of these groups:

I. Luminescent compounds.
   Carcinogenic only in cells and tissues where biological reactions give rise to ultraviolet light.
   - A. Luminescence spectra 2,900 to 3,300 A. (direct denaturation)
   - B. Luminescence spectra 3,400 to 4,500 A. (indirect action, photosensitizers necessary)

II. Compounds which are chemiluminescent during the process of metabolic breakdown.
   - A. Chemiluminescence spectra 2,900 to 3,300 A. (rare, direct denaturation)
   - B. Chemiluminescence spectra 3,400 to 4,500 A. (common, indirect action, photosensitizer necessary).

According to this hypothesis, most of the large number of otherwise heterogeneous physical and chemical carcinogens all give rise to luminous energy, which directly or indirectly (by a photosensitized process) denatures certain nucleoproteins.

SOME PROPERTIES OF THE MAMMARY TUMOR MILK AGENT. CYRUS P. BARNUM, ZELDA B. BALL, and JOHN J. BITTNER. (Divisions of Physiological Chemistry and Cancer Biology of the Department of Physiology, University of Minnesota Medical School, Minneapolis 14, Minn.)

Cell-free extracts of spontaneous mammary tumors were subjected to differential centrifugation at gravitational fields of 18,000 and 70,000 for various periods of time. Three sedimentable fractions together with the initial extract and the final supernatant fluid were injected into test animals by serial dilution. The dilutions ranged from 10^{-2} to 10^{-6}. Essentially all of the agent was sedimentable at 18,000 times gravity for a period of an hour.

NEUTRALIZATION OF MOUSE MAMMARY CANCER VIRUS WITH ANTISERUM. ROBERT G. GREEN and JOHN J. BITTNER. (Department of Bacteriology and Immunology, and Division of Cancer Biology of the Department of Physiology, University of Minnesota Medical School, Minneapolis 14, Minn.)

Antiserums have been prepared in rats and in rabbits by 5 weekly injections of cancer tissue centrifugate collected between 14,000 × gravity and 100,000 × gravity. The antiserum collected 14 days after the last injection, when mixed and incubated 2 hours with similar centrifugates of tumor tissue, neutralized them so that no tumors were formed upon inoculation of the mixture into mice. The same centrifugates were not neutralized by antiserums prepared from rats and rabbits immunized similarly against mammary tissue centrifugates, nor were they neutralized by normal rat or rabbit antiserums. It appears that the mouse mammary carcinoma milk agent is highly antigenic and this character, in addition to its small size and intracellular nature, suggests that the agent may be properly termed a virus.

EFFECT OF SODIUM FLUORIDE, DINITROPHENOL, AND LOW ENVIRONMENTAL TEMPERATURE ON THE FORMATION OF SPONTANEOUS MAMMARY CARCINOMA IN MICE. ALBERT TANENBAUM and HERBERT SILVERSTONE. (Department of Cancer Research, Michael Reese Hospital, Chicago 16, Ill.)

Caloric restriction inhibits the formation of many types of tumors of the mouse, including the mammary carcinoma. Restriction of food intake naturally results in limitation of growth of animals. Question arises as to whether inhibition of tumor formation would occur if the limitation of growth resulted from other experimental procedures; *i.e.,* chronic poisoning or increased metabolic activity. The experiment consisted of 4 groups of 50 dba females. The mice of all groups were fed 3.4 gm. of a basic laboratory ration daily. Group A was the control. To the diet of group B, 0.1 per cent sodium fluoride was added; to that of group C, 0.25 per cent dinitrophenol was added. Group D was housed in a cold room, between 41 and 55° F.; the other 3 groups were housed at an average temperature of 80° F. The approximate daily average food consumption for the 4 groups—control, NaF, dinitrophenol, and cold-room—were 3.0, 2.7, 3.3, and 3.4 gm. respectively; their general level of weight as 29, 22, 20, and 20 gm. The experiment proceeded smoothly; the mean age at death of non-tumor mice was approximately $1\frac{1}{2}$ years. By the end of the experiment (mice 99 weeks old) 74 per cent of the control mice had developed tumors; 42 per cent of the NaF group, 2 per cent of the dinitrophenol group, and 10 per cent of the group kept in the cold room. These results suggest that from a nutritional viewpoint it is not the actual amount of ingested food that is the determining factor in tumor formation, but more likely the amount of consumed food in relation to normal or special requirements.

TUMORS OF THE SALIVARY AND PARATHYROID GLANDS IN RATS FED WITH 2-ACETAMINOFLUORENE. JACOB HEIMAN. (Department of Cancer Research, College of Physicians and Surgeons, Columbia University, New York 32, N. Y.)

Wilson and his associates produced tumors in rats fed 2-acetaminofluorene mixed with food. The tumors grew in many organs and glands but none appeared in the salivary glands. Bielchowsky reported similar findings after these feeding experiments, and found tumors of the thyroid gland following the addition of thiouracil to the diet. No growths or changes were reported in the parathyroid glands.

In our experiments, 30 female and 23 male Wistar rats $2\frac{1}{2}$ to 3 months old were fed an oily mixture of 2-acetylaminofluorene by syringe and curved needle introduced into the pharynx. One c.c. of this mixture contained 10 mgm. of the drug, and later preparations 20 mgm. The total amount fed ranged between 350 mgm. to 617.5 mgm. Tumors of the submaxillary gland developed in 4 animals, of the parathyroid in 2, liver in 1, mediastinum in 1, and subcutaneous tissue of the neck in 1. Seventeen animals developed cystic tumors of the soft tissue of the neck. The cysts contained a yellow oily fluid and were surrounded by a soft capsule and pericystic adhesions. The tumors included adenocarcinoma of the submaxillary gland, sarcoma of the subcutaneous tissue, adenoma, glandular hyperplasia, and retention cysts.

The localization of these tumors in the neck, may be attributed to trauma of the pharynx and esophagus produced by the needle. The acetaminofluorene may therefore exert a local action if applied frequently to the same site. Twenty-four of the 53 animals had been fed, in addition, aromatic amino acids. None of the animals given amino acids developed any tumors after feeding with acetaminofluorene up to 650 mgm. The aromatic amino acids probably interfered with the tumor-inducing activity of acetaminofluorene.

EFFECT OF CYSTINE *PER SE* ON THE FORMATION OF HEPATOMAS IN RATS FOLLOWING THE INGESTION OF *p*-DIMETHYLAMINOAZOBENZENE. FLORENCE R. WHITE and JULIUS WHITE. (National Cancer Institute, Bethesda 14, Md.)

White and Edwards (J. Nat. Cancer Inst., 2:535-538, 1942) have shown previously that restriction of cystine in the *p*-dimethylaminoazobenzene diets of rats resulted in a prolongation of the latent period and a possible reduction in the ultimate total incidence of hepatomas. Since the animals were fed *ad libitum* and the cystine-restricted group grew less, it was not clear whether the effects achieved were due to the deprivation of cystine or to some other factor.

This report describes an experiment in which the paired-feeding technic was used to keep the food (and consequently the dye) intake of the low cystine and the cystine-supplemented rats equal. Of 48 pairs of rats, fed the low-cystine diet *ad libitum*, 45 developed hepatomas earlier than their cystine-supplemented litter mates on a restricted diet. The later appearance of hepatomas in those rats whose cystine-supplemented diet was restricted in amount is considered because of the unavoidable caloric restriction, which is also operative. The data are interpreted as indicating that cystine deprivation in itself probably exerts no effect on the formation of hepatomas due to the ingestion of *p*-dimethylaminoazobenzene and that differences observed in the earlier work may have been due primarily to differences in dosage of the dye.

BIOCHEMICAL ACTION OF COCARCINOGENS. VAN R. POTTER. (McArdle Memorial Laboratory, University of Wisconsin, Madison 6, Wis.)

The action of cocarcinogenic chemicals *in vitro* was studied in water homogenates of tissues in reaction mixtures which make it possible to measure the esterification of inorganic phosphate coupled with the oxidation of various substrates. The esterified phosphate was recovered in the form of phosphocreatine, and adenosinetriphosphate was used to link the oxidation system to the ultimate phosphate acceptor. Oxygen uptake was measured manometrically. Calcium ions were found to effect a considerable decrease in the net yield of esterified phosphate, at concentrations considerably below the level of serum calcium. Compounds that have cocarcinogenic activity also decreased the yield of esterified phosphate, but no correlations between cocarcinogenic activity and action *in vitro* have been attempted. However, the action of calcium ions suggests that physical cocarcinogens could act through the same fundamental mechanism as the chemical cocarcinogens and result in a derangement of the phosphate balance.

NARCOTIZING AGENTS AND PULMONARY TUMORS IN MICE. C. D. LARSEN. (National Cancer Institute, Bethesda 14, Md.)

Ethyl carbamate initiated or accelerated the development of pulmonary tumors in mice. The susceptibility of several strains of mice to pulmonary tumor induction by this agent paralleled their susceptibility to spontaneous pulmonary tumor formation. Homologues of ethyl carbamate, *i.e.*, the methyl, propyl, butyl, iso-amyl, and phenyl esters, uniformly and strikingly failed to elicit pulmonary tumor formation. Alkylated derivatives of urethane, administered intraperitoneally to mice, elicited the development of pulmonary tumors, but to a lesser degree than unsubstituted ethyl carbamate. The degree of activity of the substituted derivatives was much less than that of ethyl carbamate and varied inversely with the extent of alkylation. Administration of a series of diurethanes led to the development of multiple lung tumors. These compounds approached ethyl carbamate, from which they were derived, in potency.

Induction of narcosis in mice by urethane appeared to be unrelated to the ability of this agent to incite the development of pulmonary tumors. Repeated administration of sub-narcotizing doses elicited multiple lung tumors. Conversely, a series of compounds not related to urethane, repeatedly administered in doses that induced deep narcosis, failed to increase the pulmonary tumor incidence above that in control mice.

THE NEOPLASTIC POTENTIALITIES OF TRANSPLANTED EMBRYO TISSUE: THE GASTRIC AND PULMONARY TUMORS INDUCED WITH METHYLCHOLANTHRENE. WILLIAM E. SMITH and PEYTON ROUS. (Laboratories of The Rockefeller Institute for Medical Research, New York 21, N. Y.)

As already reported, tumors swiftly arise from the epidermis of C mouse embryos, after transfer to the muscle of adults together with olive oil containing methylcholanthrene and Scharlach R. Many of the cancers are transplantable. Fragments of embryo stomachs form cysts in the muscle, which enlarge as mucus or keratin accumulates. Their epithelial lining flourishes, and the glands secrete rennin and pepsin, but no hydrochloric acid although parietal cells are numerous. Tumors fail to appear. However, when oil containing methylcholanthrene and Scharlach R has been introduced with the tissue, growths soon arise—papillomas and squamous cell carcinomas from the squamous portion of the stomach, and adenoacanthomas and squamous cell carcinomas from the glandular portion—as if by metaplasia, but no adenocarcinomas develop. Several of the cancers have been propagated.

Embryo lung tissue lives long and differentiates well in the muscle, forming alveoli with flattened epithelium. It encysts less of the carcinogen than does the embryo stomach, yet multiple adenomas appear after a few weeks and carcinomas, later. Some have been transferred. No tumors arose from control implants.

Nearly all the gastric and pulmonary neoplasms have resembled those occurring in adult mice. Certain squamous cell carcinomas have had characters traceable to their origin and differentiating them from tumors in the same category derived from the epidermis.

SIGNIFICANCE OF DOSAGE OF CARCINOGEN IN EVALUATING EXPERIMENTAL PROCEDURES. ALBERT TANNENBAUM and HERBERT SILVERSTONE. (Department of Cancer Research, Michael Reese Hospital, Chicago 16, Ill.)

It has been assumed by many who have worked with induced tumors that the use of massive doses of carcinogen masks effects that may be expected from an experimental procedure. The inhibiting effect of caloric restriction and the augmenting effect of a fat-enriched diet on the formation of skin tumors induced by benzpyrene are phenomena that permit partial testing of this question. Employing both moderate and "massive" dosages of carcinogen the effects of these two dietary changes were investigated. Eight groups of 50 mice were used. Two groups were given a calorie-restricted diet; one of these received moderate dose of carcinogen, the other, "massive." Similarly two groups were fed a high fat diet, one given moderate dose of carcinogen, the other, "massive." Each of these four groups had its own control. The effect of the dietary treatments were evaluated from both the standpoint of percentage of mice developing tumors and the mean time of appearance of tumors. The results are summarized as follows: Variations in tumor incidence observed with moderate dosage of carcinogen were obliterated by the "massive" dosage. In contrast, however, the "massive" dosage emphasized the differences in the mean time of appearance of the tumors. It is suggested that in some instances, the effects of treatment may be brought out by massive dosages of carcinogen and consideration of the consequent data on time of appearance of the tumors.

CHARACTERISTICS OF THE SYMPATHICOBLASTOMA CULTIVATED *IN VITRO*. MARGARET R. MURRAY and ARTHUR PURDY STOUT. (College of Physicians and Surgeons, Columbia University and Presbyterian Hospital, New York 32, N. Y.)

Biopsy material, either primary or metastatic, was obtained from eight patients and explanted in hanging-drops by the Maximow method. The sympathicoblasts tended to cohere in clumps composing a very friable tissue, which broke up when cut or mechanically disturbed, so that in setting out the cultures many clumps of varying sizes were scattered through the medium. Within 24 hours some of the small round or oval neuroblasts composing these clumps had produced neurites of varying lengths, easily recognizable and quiet distinct from any form of outgrowth produced *in vitro* by non-nervous tissues. The sympathicoblasts were usually monopolar. Necrosis among the outer rim of cells composing a clump was so common as to be characteristic. The living cells stained readily with neutral red applied supravitally in 1/10,000 dilution. The faculty, coupled with the necrosis and the production of neurites within 24 hours, provides a quick and certain means of differential diagnosis between this tumor of nervous origin and the lymphosarcoma with which it is sometimes confused clinically. When cultivated *in vitro* the tumor becomes exceedingly easy to diagnose.

Cultures may be maintained for weeks or months, during which time the neurites become longer and more numerous, sometimes ramifying to form plexuses. The Bodian protargol and gold chloride impregnation method when applied to whole mounts of the material provides sharp and satisfactory permanent preparations.

THE INDUCTION OF GERMINAL MUTATIONS BY METHYLCHOLANTHRENE. LEONELL C. STRONG. (Department of Anatomy, Yale University School of Medicine, New Haven 11, Conn.)

Forty-two germinal mutations involving coat color, structure, eye pigmentation, and behavioristic patterns have occurred in the descendents of mice receiving methylcholanthrene. The mutation rate is approximately one to two thousand mice; in the untreated controls the mutation rate has been approximately one in twenty-six thousand mice. In addition to these proven germinal changes there have been other biological effects such as precocious sexual maturity, precocious senility, alterations in cancer susceptibility, fertility and sterility, excessively large first litters, disturbances of embryonic development, such as *situs inversus,* dextrocardia, imperforate vaginas, and other abnormalities.

STUDIES OF THE EFFECTS OF GENES AND THEIR RELATION TO THE DEVELOPMENT OF MAMMARY CARCINOMA IN THE MOUSE. WILLIAM S. MURRAY. (New York State Institute for the Study of Malignant Diseases, Buffalo 3, N. Y.)

The analysis of 18 crosses between high cancer dilute brown and low cancer C57 black mice, in which varying concentrations of the dilute brown and the black chromatin were obtained, indicates that the development of mammary carcinoma in mice is not a manifestation of the presence of a specific gene or genes in the chromatin, and that the role of genetics and of the genetic method, in cancer research, is in the development of physiologies, favorably disposed to the study of extrinsic factors.

THE INFLUENCE OF TESTOSTERONE ON THE GROWTH OF DEER ANTLERS. JOSEPH C. AUB and GEORGE WISLOCKI. (Medical Laboratories of the Collis P. Huntington Memorial Hospital, and The Harvard Medical School, Boston, Mass.)

In a previous report we showed the characteristics and rate of growth of deer antler. Subsequently, we have attempted to alter the usual characteristics by the injection of testosterone propionate at various times during the growing season. The injection of this hormone into a castrate female resulted in the growth of good sized antlers; when injected into bucks in July it resulted in abnormally early maturation of the antlers; and it caused a prompt maturation in castrated bucks, which would not otherwise have occurred. This hormone appears to produce stimulation of growth and also to have a dramatic effect in producing maturity of the antlers.

ELECTRON MICROSCOPY OF NORMAL AND MALIGNANT CELLS. KEITH R. PORTER and EDWARD G. PICKELS. (The Rockefeller Institute for Medical Research, and the International Health Division, The Rockefeller Foundation, New York 21, N. Y.)

An earlier report described the development of technics by which cultured cells can be prepared for electron microscopy. By these procedures it is possible to define details of cell structure, especially those of the cytoplasm, which are well below the resolving power of the light microscope. The interpretation of such detail presents numerous problems but enough progress has been made in this respect to warrant the preliminary examination of malignant cells. Specifically, the "microcytology" of cells from 3 different rat sarcomas have been compared with that of normal cells of similar origin and similarly cultured. The most prominent differences noted have been in that portion of the cell designated as endoplasm. This material in normal cells usually appears as a reticulum with small vesicles (50 to 100 mμ) along the strands. In malignant cells it presents the same form but is greatly hypertrophied, is more finely divided, and shows a scattering of dense strands of particular interest, as well. The mitochondria in malignant cells tend to be more numerous and smaller, but so far no abnormalities of structure have been detected. Fat bodies are not unlike those in normal cells. Continued examination of this and similar material will probably reveal additional differences, as well as point to the significance of those already noted.

ELECTRON MICROSCOPE STUDY OF CHICKEN TUMOR CELLS. ALBERT CLAUDE, KEITH R. PORTER, and EDWARD G. PICKELS. (The Rockefeller Institute for Medical Research, and the International Health Division, The Rockefeller Foundation, New York 21, N. Y.)

A number of fowl tumors are transmissible by filter-passing agents. In the present work advantage was taken of a recently devised method, which permits the examination of tissue culture cells in the electron microscope, and the presence and distribution of the causative agents in chicken tumor cells was investigated. Two different tumors, namely, chicken tumor I and chicken tumor 10 have been studied. Small bodies thought to represent the tumor agents, and so far not detected in normal homologous chicken cells, have been found in variable abundance in cultured cells derived from both tumors. They appear in small clusters, sometimes in groups of 2, and most frequently isolated and scattered. In some cases, they seem to lie at the surface, or just beneath the surface of the cell. They are also found outside the cells, especially in the neighborhood of those that have disintegrated. The small bodies of chicken tumor cells are readily distinguishable from normal cell constituents by their regular granular shape, their relatively uniform size, and because of a greater density in osmium-fixed preparations. The size of these small bodies, as estimated by measurements on enlarged micrographs, range roughly between 70 and 100 mμ, values that are in close agreement with the size previously attributed to the chicken tumor agents by means of centrifugation and filtration methods.

AN *IN VITRO* STUDY OF THE CELLS OF SEVEN *IN VITRO* GENERATED STRAINS OF C3H MOUSE SARCOMAS. EMMA SHELTON and WILTON R. EARLE. (National Cancer Institute, Bethesda 14, Md.)

As previously described by Earle and his co-workers, 7 strains of sarcoma cells (HW, D, H. J. L. N. and O) were generated from a single strain of C3H mouse fibroblasts *in vitro*. These cell strains gave rise on injection to 7 corresponding strains of sarcomas. After 99 to 931 days *in vivo,* these tumors strains were recultured *in vitro*.

Cultures of all strains progressed toward a fairly stable architecture by the fourth to sixth generations *in vitro*. This stabilized architecture was roughly comparable to that seen in the corresponding culture strains, which had never been injected into mice. However, the cells of strain J, originally treated for 32 days with 20-methylcholanthrene, showed a series of unusually complex alterations. In the first generation culture there was a wave of multinuclear giant cell production, but they apparently died. In the second and third generations practically all cells of some of the cultures assumed a very large size, were usually mononuclear, and had large oval nuclei and large nucleoli, and were disappearing by the sixth generation. These peculiar alterations in the cells of strain J augment other data, which suggest that at this stage of cell transformation under methylcholanthrene treatment (32 days) the cells are in a peculiarly unstable condition.

On re-injection into mice, all strains, with the exception of strain J, gave rise to sarcomas.

INCREASED ACTIVITY OF THE HODGKIN'S DISEASE FACTOR BY SERIAL TRANSPLANTS IN TISSUE CULTURE. C. G. GRAND, and GLADYS CAMERON. (New York University and St. Vincent's Hospital, New York, N. Y.)

Lymph nodes removed surgically from patients with Hodgkins disease were ground in buffer solution, 0.005 M at pH 7.2. After high speed fractionation by ultra centrifugation, the cell-free sediment was suspended in 0.5 per cent serum hydrolysate at pH 7.0. This suspension was inoculated into tissue cultures of chick spleen and serial transfers of the cultures made, the period of the intervals of transfer decreasing from 10 to 5 days. At each transfer a part of the culture was fixed and stained while the other part was minced and added to a fresh culture of normal chick spleen. The technic was varied by transferring only the supernatant cell-free liquid medium of the previous culture. Disintegration of the cells in the cultures increased with each of the 12 serial transfers which have been made to date. The stained preparations gave indications of increasing numbers of cellular inclusions.

THE USE OF HETEROLOGOUS TRANSPLANTS AS AN AID TO THE DIAGNOSIS AND CLASSIFICATION OF HUMAN TUMORS. HARRY S. N.

GREENE. (Department of Pathology, Yale University School of Medicine, New Haven 11, Conn.)

For several years, transfer to the anterior chamber of the guinea pig's eye has been used as an adjunct to the microscope in the study of human tumors of questionable classification. The ability to survive in the foreign environment is not shared by adult tissues, benign tumors or chronic granulomas and the mere fact of growth immediately distinguishes the tissue as cancer. In addition, growth in the pig's eye is usually associated with a higher degree of cellular differentiation and structural organization than that which characterizes the human tumor, and permits a more precise classification of anaplastic growths than is warranted by the morphology of the biopsy specimen.

PRELIMINARY STUDIES ON THE RECOVERY OF THE ROUS SARCOMA VIRUS FROM GUINEA PIG TISSUES DURING GROWTH OF THE TUMOR IN THE ANTERIOR CHAMBER OF THE RODENT'S EYE. EDWARD W. SHRIGLEY. (Department of Bacteriology, Yale University School of Medicine, New Haven 11, Conn.)

Following the observation that the Rous sarcoma will grow in the anterior chamber of the guinea pig's eye, two important problems present themselves. One concerns the effect of the mammalian host upon the chicken tumor virus, and the other, the effect of the Rous agent upon the guinea pig host. Regarding the first, it has been shown that there may be an alteration of tissue and species specificities of the virus as a result of its residence in the guinea pig. Of the latter problem, it is evident that while no tumors have been found in the guinea pig at sites other than the eye following intraocular inoculation, the Rous virus does not remain localized to this area. It is possible to obtain sarcomas in chicks by the inoculation of various tissues from guinea pigs possessing intraocular transplants of the Rous sarcoma.

Guinea pigs that had received anterior chamber transplants of the Rous sarcoma were killed at varying times following their inoculation. The spleen, liver, lung, lymph nodes, and whole blood of the animals were tested separately for the presence of the virus by the injection of these materials into chicks 1 or 2 weeks old. In these birds sarcomas of the Rous type were obtained from ground spleens of guinea pigs killed from 24 hours to 8 days after transplantation. Ground livers were positive for virus on the second and fourth days only, and superficial cervical lymph nodes adjacent to the inoculated eye were positive on the third and sixth days only. Lungs and blood have not yielded positive results. Lung material was passed by trocar.

TRANSPLANTABILITY OF INDUCED GRANULOSA CELL TUMORS AND OF LUTEOMA IN MICE AND SECONDARY EFFECTS OF THESE GROWTHS. J. FURTH. (Cornell Medical College, New York 21, N. Y.)

Eleven ovarian tumors, induced by x-rays have been transmitted in successive passages to mice of both sexes. Eight were of the granulosa cell type, 2 were luteomas and 1 was a tubular adenoma. Histological changes indicate that cells of at least 2 transplantable strains secrete estrogens. Mice bearing tumors of these strains have also a cavernous dilatation of the sinusoids of the liver, spleen, and adrenals, and associated with this there appears to be a great increase in blood volume. These alterations may be caused by abnormal products, possibly steroid hormones, of the tumor. Cells of the transmissible luteomas multiply by mitotic division and retain their distinctive features in mice of both sexes throughout numerous passages. Mice bearing large luteomas of strain IX exhibit a profound atrophy of the adrenal cortex, and the animals gain weight by deposition of fat in the normal fat depots.

A STUDY OF THE ORGANOPHILIC TENDENCIES OF TWO TRANSPLANTABLE MOUSE TUMORS. ARTHUR M. CLOUDMAN. (Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Me.)

Mice of the leaden strain do not have a high frequency of spontaneous tumors. Many of the tumors that do occur involve the livers of the hosts. Two typical liver tumors from this strain were discussed and comparison made of the host-tumor relationship that is established by each tumor subsequent to its transplantation.

A carcinoma (C954) remains localized at the site of implantation. However, a reticuloendothelioma (C198) shows definite organophilic tendencies that vary according to the type of host receiving the implant.

A SPONTANEOUS, TRANSPLANTABLE TESTICULAR TUMOR IN A MOUSE. C. W. HOOKER, L. C. STRONG, and C. A. PFEIFFER. (Department of Anatomy, Yale University School of Medicine, New Haven 11, Conn.)

A unilateral testicular tumor resembling the most advanced type seen in estrogen-treated mice was found in an untreated mouse of the Strong C strain. The contralateral testis contained a small intertubular nest of cells identical with those comprising the tumor. No metastatic growths were found, and the remainder of the genital system was normal.

The tumor was transplanted into mice of the same strain and has been carried through 10 transfer generations. In the first two, large grafts were present after 38 and 29 weeks. In later transfers, large grafts were present after 3 to 6 weeks. The tumor was carried through six transplant generations in estrogen-treated hosts also, the first showing a large graft within 29 weeks and the later generations showing large grafts at 11 weeks or less. After 2 and 3 transfers in estrogen-treated hosts, untreated hosts had large grafts after 28 weeks, whereas administration of estrogen resulted in large grafts within 11 weeks. After two transfers in untreated hosts the administration of estrogen had no influence on the growth of transplants. The transplants growing in untreated hosts were composed of cells identical with those of the original tumor. In estrogen-treated hosts the cells comprising the transplants were smaller and less differentiated than those of the original tumor.

MICROMANIPULATION STUDIES ON THE PHYSIOLOGICAL REACTIONS OF MUSCLE ELEMENTS IN RHABDOMYOSARCOMA. C. G. GRAND. (New York University and St. Vincent's Hospital, New York, N. Y.)

The problem was to determine whether myosarcomatous cells of induced mouse rhabdomysarcoma retain the property of muscular contractility exhibited by normal embryonic muscle cells.

The tumors were produced in C3H strain mice by introducing methylcholanthrene pellets into the leg muscles. Large tumors developed at the site of the pellets and the tumors that proved to be true rhabdomyomas were grown in tissue culture. As controls, mouse embryonic muscle tissue was used. Within 48 hours, both the tumor and normal muscle fragments showed extensive out-growth of myoblasts and multinucleated muscle fibers. However, in the tumor outgrowth, the number of multinucleated fibers was not as great as those in the embryonic tissue.

By means of micromanipulation, the contractility of the muscular elements was tested by prodding with microneedles and by electrical stimulation (inductorium) with microelectrodes.

It was found that the multinucleated muscle fibers of the tumor would contract both to prodding with microneedles and to electrical stimulation, whereas the mononucleated myoblastic cells would react only to electrical stimulation and not to prodding. This result is similar to the reactivity of normal embryonic muscle cells grown in tissue cultures and indicates that the muscle elements in rhabdomyosarcoma retain the physiological activity of contractility found in normal embryonic muscle tissue.

ADRENAL MEDULLARY TUMOR (PHEOCHROMOCYTOMA) IN THE GOLDEN HAMSTER (*CRICETUS AURATUS*). RUTH E. SHRADER. (Department of Anatomy, Yale University School of Medicine, New Haven 11, Conn.)

A right adrenal medullary tumor measuring approximately 8 mm. in diameter was found at autopsy in an apparently normal senile (18 months) male golden hamster. The tumor was a cream-colored, firm mass, which compressed the upper pole of the right kidney. The other adrenal appeared normal. Nutmeg liver, and shrunken, hyperemic spleen were found upon gross examination. Microscopically it was found that the tumor had displaced all of the cortical elements except for a thin cap at the anterior pole. Invasion of the cortical layer by tumor cells was evident. The tumor was not encapsulated. The cytoplasm of the tumor cells had a delicately fibrillar appearance, their nuclei were round and vesicular with a fine, chromatin network and prominent nucleoli. The cells were tightly packed and of irregular shape, and were arranged in acini or broad sheets. The connective tissue stroma was scanty and highly vascular. There was approximately 1 mitotic figure for each high power field. No evidence of metastasis was found; the left adrenal cortex appeared normal; the medullary cells of the adrenal were pale and vacuolated; the spleen and liver showed considerable venous congestion; the central hepatic cells showed cloudy swelling, the peripheral cells were vacuolated, and there were numerous Kupfer cells containing much hemosiderin.

SALIVARY GLAND TUMORS, ADAMANTINOMAS AND CRANIOPHARYNGIOMAS: ANLAGE TUMORS. BÉLA HALPERT. (Department of Pathology, University of Oklahoma School of Medicine, Oklahoma City, Okla.)

A series of tumors of the salivary gland, the one of adamantinomas and another of craniopharyngiomas, were studied for their cellular and structural patterns, gross characteristics, and sites of occurence. The data thus collected suggest that all are derived from embryonal rests of the ectoderm. The structural differences may be attributed in part to the stage of evolution of the cell rests at the time of separation from the ectodermal anlage, and partly to influences of the environment on the tumors in their respective sites. The salivary gland tumors appear to be the oldest genetically. The group of cells from which they originate must have separated from the ectoderm at the stage when they had as yet not acquired their dominant characteristics as ectodermal or mesodermal cells; hence their capacity to differentiate into ectodermal and mesodermal tissues. This explains the variations in their structural patterns, their "mixed" appearance. It also explains the apparent transformation of one kind of tissue into another such as the gradual transition of what appear to be epithelial cells into hyaline cartilage. Adamantinomas and craniopharyngiomas are evidently of more recent genetic origin; hence their simpler range of variation in cellular patterns. The stroma in these growths is a contribution of the surrounding connective tissue, whereas in tumors of the salivary gland it is a part of the neoplasm.

EXPERIMENTAL LIVER CANCER IN RATS BY BUTTER YELLOW. J. Z. STA. CRUZ. (College of Medicine, University of the Philippines, Cancer Institute, Philippine General Hospital, and St. Luke's Hospital, Manila, P. I.)

Primary carcinoma of the liver, a problem of the Oriental countries, is reproduced in albino rats of the Wistar strain by feeding with polished rice coated with butter yellow (dimethylaminoazobenzene). The diet of the rats in this experiment was prepared purely from local products to conform with our present diets. The varied types of liver lesions during the different periods of the experiment, serous hepatitis, adenomatosis (bile duct adenoma), cirrhosis, and carcinoma (hepatoma), were found interesting and instructive. The administration of yeast and butter yellow together with the basal diet was tried in a group of rats, also.

American Association for Cancer Research, Inc.

37th Annual Meeting

Hotel Ambassador, Atlantic City, New Jersey
March 10 and 11, 1946

Proceedings of Business Sessions

Minutes of the Meeting of the Board of Directors Held March 10, 1946

The Board of Directors met at the Ambassador Hotel in Atlantic City, New Jersey. Drs. Bittner, Cowdry, Doisy, Gardner, Huggins, Murphy, Shear, and Warren were present.

It was voted that the minutes of the previous meeting be approved as published in *Cancer Research,* 1945, Volume 5, pages 595-598.

REPORT OF OFFICERS

The report of the treasurer was read. In the absence of Dr. W. H. Woglom, the chairman appointed Dr. J. B. Murphy auditor.

REPORT OF COMMITTEES

Program Committee.—Chairman M. J. Shear reported the receipt and scheduling for presentation of an unexpectedly large number of papers. The problem of how best to arrange future programs was raised. The most urgent questions were whether the number of papers presented should be limited, whether the requirements for abstracts should be made more stringent, and whether a long meeting with single sessions or a shorter meeting with concurrent sessions is preferable. It was recommended that the Committee draw up recommendations on these questions.

Nominating Committee.—Chairman W. U. Gardner reported that his Committee had nominated for members of the Board of Directors to serve until 1949: Drs. J. C. Aub, E. V. Cowdry, E. A. Doisy, J. B. Murphy, E. P. Pendergrass, H. P. Rusch, Albert Tannenbaum, and H. C. Taylor, Jr. These names were listed on the proxies sent to the members of the Association by the Acting Secretary.

Membership Committee.—In the absence of the Chairman, Dr. W. H. Woglom, Dr. Charles Huggins reported that the Association now has 475 active members and 8 emeritus or honorary members.

The nominations for active membership were read. Fifty candidates were elected. They were:

Albert, Samuel, M.D., McGill University, Montreal 2, Quebec, Canada.

Biesele, John J., Ph.D., Sloan-Kettering Institute for Cancer Research, 444 East 68th Street, New York 21, N. Y.

Bothe, Albert E., M.D., D.Sc., 255 South 17th Street, Philadelphia 3, Pa.

Boutwell, R. K., Ph.D., McArdle Memorial Laboratory, University of Wisconsin, Madison 6, Wis.

Cantarow, Abraham, M.D., Jefferson Medical College, 1025 Walnut Street, Philadelphia 7, Pa.

Clarke, B. Earle, M.D., Rhode Island Hospital, Providence 2, R. I.

Costello, Cyril J., M.D., St. Louis City Hospital, 1515 Lafayette Avenue, St. Louis 4, Mo.

Daniel, George E., Sc.D., National Cancer Institute, Bethesda 14, Md.

Davis, Harry A., M.D., College of Medical Evangelists, Boyle and Michigan Avenues, Los Angeles 33, Calif.

Dische, Zacharius, M.D., College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York 32, N. Y.

Drabkin, David L., M.D., University of Pennsylvania School of Medicine, Philadelphia 4, Pa.

Dunn, Thelma B., M.D., National Cancer Institute, Bethesda 14, Md.

Engle, Earl T., Ph.D., College of Physicians and Surgeons, Columbia University, 630 W. 168th Street, New York 32, N. Y.

Evans, Virginia John, Sc.D., National Cancer Institute, Bethesda 14, Md.

Friedgood, Harry B., M.D., 1943 Queensbury Drive, Los Angeles 34, Calif.

Gonzalez, Abraham Ayala, M.D., Plaza de la Republica No. 46, Mexico City, Mexico.

Gopal-Ayengar, A. R., Ph.D., Barnard Free Skin and Cancer Hospital, Washington and Theresa Avenues, St. Louis 3, Mo.

Green, Elizabeth Ufford, Ph.D., Lankenau Hospital Research Institute, Girard and Corinthian Avenues, Philadelphia 30, Pa.

Green, Robert G., M.D., University of Minnesota, Minneapolis 14, Minn.

Griswold, Matthew H., M.D., Dr. P.H., Connecticut State Department of Health, 165 Capitol Avenue, Hartford, Conn.

Hastings, A. Baird, Ph.D., Sc.D., Harvard Medical School, 25 Shattuck Street, Boston 15, Mass.

Haymaker, Webb, M.D., 1567 Willard Street, San Francisco, Calif.

Homberger, Freddy, M.D., Memorial Hospital, York Avenue at 68th Street, New York 21, N. Y.

Hoster, Herman A., M.D., Kinsman Hall, Ohio State University, Columbus, Ohio.

Huseby, Robert A., M.D., University of Minnesota, Minneapolis 14, Minn.

Lan, Tien Ho, Ph.D., University of Rochester School of Medicine and Dentistry, Rochester 7, N. Y.

LEACH, JOHN E., M.D., Memorial Hospital, York Avenue and 68th Street, New York 21, N. Y.
LEPAGE, G. A., PH.D., McArdle Memorial Laboratory, University of Wisconsin, Madison 6, Wis.
LEUCHTENBERGER, MRS. CECELIE, Mount Sinai Hospital, Fifth Avenue and 100th Street, New York 29, N. Y.
MACCARDLE, Ross C., PH.D., Washington University School of Dentistry, St. Louis 10, Mo.
MACDONALD, ELEANOR J., A.B., Connecticut State Department of Health, 165 Capitol Avenue, Hartford, Conn.
MCCAWLEY, ELTON L., PH.D., Yale University School of Medicine, New Haven 11, Conn.
MILLER, ELIZABETH C., PH.D., McArdle Memorial Laboratory, University of Wisconsin, Madison 6, Wis.
MIRO-QUESADA, OSCAR, JR., M.D., Paseo Colon 201, Lima, Peru, S. A.
MURPHY, EDWIN D., M.D., University of Tennessee School of Medicine, Memphis 7, Tenn.
MYERS, WILLIAM G., PH.D., M.D., College of Medicine, Ohio State University, Columbus 10, Ohio.
PAPANICOLAOU, GEORGE N., M.D., Cornell University Medical College, 1300 York Avenue, New York 21, N. Y.
PASCHKIS, KARL E., M.D., Jefferson Medical College, 1025 Walnut Street, Philadelphia 7, Pa.
PORTER, KEITH R., PH.D., The Rockefeller Institute for Medical Research, 66th Street and York Avenue, New York 21, N. Y.
RITCHEY, MARY G., M.D., Barnard Free Skin and Cancer Hospital, Washington and Theresa Avenues, St. Louis 3, Mo.
SCHEELE, LEONARD A., M.D., National Cancer Institute, Bethesda 14, Md.
SCHLUMBERGER, HANS G., M.D., University of Pennsylvania, School of Medicine, Philadelphia 4, Pa.
SMITH, FERN W., PH.D., Yale University School of Medicine, New Haven 11, Conn.
SPRUNT, DOUGLAS H., M.D., University of Tennessee Medical School, Memphis 7, Tenn.
STEELE, ROBERT, PH.D., McArdle Memorial Laboratory, University of Wisconsin, Madison 6, Wis.
TAFFEL, MAX, M. D., Yale University School of Medicine, New Haven 11, Conn.
TULLIS, JAMES LYMAN, M.D., New England Deaconess Hospital, Deaconess Road, Boston, Mass.
VAN DYKE, JOHN H., PH.D., Washington University School of Medicine, Euclid Avenue and Kingshighway, St. Louis 10, Mo.
WICKS, LESTER F., M.S., Barnard Free Skin and Cancer Hospital, Washington and Theresa Avenues, St. Louis 3, Mo.
WILSON LOUISE PALMER, PH.D., Wellesley College, Wellesley, Mass.

One nomination for contributing membership was presented and approved. He is:

COL. J. E. ASH, Army Institute of Pathology, Washington, D. C.

Two members were, on application, transferred to emeritus membership. They were:

WILLIAM H. WOGLOM, M.D., College of Physicians and Surgeons, Columbia University, New York 32, N. Y.
ARTHUR E. HERTZLER, M.D., Hertzler Clinic, Halstead, Kans.

The death of one member, Dr. William Cramer, Barnard Free Skin and Cancer Hospital, St. Louis 3, Missouri, was announced with regret.

Journal Committee.—Chairman J. B. Murphy reported that *Cancer Research* continues to be supported by The Jane Coffin Childs Memorial Fund for Medical Research, The Donner Foundation, The Anna Fuller Fund as well as by an assessment of one dollar per member of the Association. He urged the desirability of the Association's eventually assuming greater responsibility for financing and managing the journal.

The editorship of Dr. William H. Woglom was warmly commended.

Dr. Murphy pointed out that foreign appeals for back numbers cannot be met, and suggested that supplying this need merits the support of foundations interested in cancer research.

Various means of the Association's financing the journal were discussed. Although the annual cost is approximately $10,000, there was much sentiment that the present practice of the Association's furnishing one dollar per member is all that is justified at present. It was voted that, "In order that the Association may plan intelligently to increase its support to the journal the Board of Directors requests that a statement of the financial condition of the journal be made available before the next meeting of the Board."

International Cancer Research Congress Committee.—Chairman M. J. Shear reported that informal discussions and correspondence with investigators in this country and abroad indicate a preference for a congress being held in September, 1947 in the United States. After discussion is was voted that, "The Committee be empowered to investigate the question by consulting investigators in several nations, particularly with respect to the problems of facilities and time." It was also voted that, "The Committee be empowered to inquire into the costs of past International Cancer Research Congresses."

UNFINISHED BUSINESS

After discussion of the proposal made at the last meeting to consider the desirability of a committee to serve as a clearing house for conferences, it was voted to table the question without action.

NEW BUSINESS

The count of the proxies for new members of the Board of Directors was reported by the Acting Secretary. The nominees receiving the largest numbers of votes were Drs. J. C. Aub, E. V. Cowdry, E. A. Doisy, and H. C. Taylor, Jr. It was voted, "That the Acting Secretary cast one ballot for the election of Directors as revealed by the count of the proxies." The ballot was cast and the Directors were declared elected.

It was voted, "That the expenses of the Program Committee in arranging the program for the annual meeting be paid from the treasury."

It was voted, "That expenses incurred in conducting the annual meeting be met."

The meeting adjourned at 11:40 p. m.

The meeting of the Board was reconvened on March 11, 1946 at 8:20 a. m. Present were Directors Bittner, Cowdry, Furth, Gardner, Shear, and Warren.

For the nomination of new officers it was voted that "The entire Board of Directors act as a nominating committee."

The nominations of the following officers for the next year were then made: For President, William U. Gardner; for Vice-President, John J. Bittner; for Acting Secretary-Treasurer, Charles W. Hooker.

To fill the unexpired term of Dr. William H. Woglom as member of the Board of Directors, Dr. Austin M. Brues was nominated and elected.

The meeting was adjourned at 8:45 a. m.

SHIELDS WARREN,
Chairman, Board of Directors
CHARLES W. HOOKER,
Acting Secretary

MINUTES OF THE MEETING OF THE MEMBERS HELD MARCH 11, 1946

A meeting of the members of the Association was held at the Ambassador Hotel, Atlantic City, New Jersey, with President Shields Warren in the chair.

Reading of the minutes of the previous meeting was waived inasmuch as they were published in *Cancer Research*.

The reports of the Acting Treasurer and the Auditor for the Board of Directors were presented and approved.

The nominations for officers of the Association made by the Board of Directors were read:

WILLIAM U. GARDNER, *President*
JOHN J. BITTNER, *Vice President*
CHARLES W. HOOKER, *Acting Secretary-Treasurer*

It was voted that, "The Secretary cast one ballot for each of the nominees." The ballot was cast and the officers were declared elected.

The list of newly elected members was read by the Acting Secretary. These names are recorded in the minutes of the meeting of the Board of Directors on March 10, 1946.

There being no further business, the meeting adjourned.

SHIELDS WARREN,
President
CHARLES W. HOOKER,
Acting Secretary

MINUTES OF THE MEETING OF THE BOARD OF DIRECTORS HELD MARCH 11, 1946

The meeting was called at 11:00 p. m. in the Ambassador Hotel in Atlantic City, New Jersey, following waiver of previous formal notice of the meeting of the Directors, signed by all Directors present and constituting a quorum. Present were Directors J. C. Aub, J. J. Bittner, A. M. Brues, E. V. Cowdry, Jacob Furth, W. U. Gardner, M. J. Shear, and Shields Warren.

It was voted, "That the reading of the minutes of the previous meeting be waived."

The question of the desirability of not limiting the membership of standing committees to members of the

March 1, 1946

Cash on hand (Union & New Haven Trust Co.) July 3, 1945		$1640.63
Cash on hand (Greenwich Savings Bank) Jan. 1, 1945		625.70
Interest on Savings Account to January 1, 1946		9.40
Collections July 3, 1945—March 1, 1946		1178.60
Secretarial service, 1945-1946	$100.00	
Rubber stamps	1.43	
File drawer	3.40	
Letterheads, billheads, nomination forms	43.55	
Printing—notices of meeting, ballots	37.00	
Stamps	30.06	
Bank charges—exchange on Canadian checks	1.86	
Cancer Research—subscriptions through secretary's office	10.00	
Refund on overpaid dues	3.00	
	$230.30	$3454.33
Balance on hand March 1, 1946		3224.03
Accounts receivable		473.00
		$3697.03

CHARLES W. HOOKER, *Acting Secretary-Treasurer*

I hereby certify that the accounts and vouchers in the American Association for Cancer Research, Inc., for the above recorded period, have been examined by me, and that the above are true statements of its financial operations and of its financial conditions as of March 1, 1946.

JAMES B. MURPHY, *Auditor for the Directors*

President Warren announced that in accordance with the By-Laws, Article II, Section 6, Dr. Austin M. Brues had been elected to serve the remainder of the term of office of Director William H. Woglom who had resigned. The new Directors chosen to serve until 1949 were also announced.

Board of Directors was raised. It was agreed that only the Chairmen need be directors, and that this arrangement is permitted by the By-Laws. The Chairman of the Board proposed the following committees:

Journal Committee.—M. J. Shear, *Chairman;* S. Bayne-Jones, M. W. S. Schram.

Membership Committee.—Charles Huggins, *Chairman;* Jacob Furth, A. M. Brues.

Nominating Committee.—H. C. Taylor, Jr., *Chairman;* H. B. Andervont, E. A. Doisy.

Program Committee.—J. J. Bittner, *Chairman;* J. C. Aub, J. P. Greenstein.

It was voted, "That the Board approve the proposed committees."

The chairman of the previous committee on an International Cancer Research Congress, Dr. M. J. Shear, reported that he wished to be relieved of this responsibility. Preliminary inquiries in this country and abroad disclosed a desire for an international congress. The earliest feasible date suggested is September, 1947, and a majority of the investigators consulted favor the United States as a site for the meeting. It was agreed that the Chairman of the Board of Directors should appoint a committee to study the question and make recommendations.[1]

It was voted, "That the Committee on Cancer Research, its Organization and Support, proposed at earlier meetings, be activated as a standing committee." The Chairman of the Board proposed the following committee: G. M. Smith, Charles Huggins, and Shields Warren, *Chairman.* The Board recommended that the Committee examine the possibility that the Association or its Board of Directors through this Committee might properly serve in keeping before the membership facilities afforded for the support of cancer research.

NEW BUSINESS

It was unanimously resolved, "That Charles W. Hooker, Acting Secretary-Treasurer and William U. Gardner, President, be, and each of them hereby is authorized, in the name and on behalf of the Corporation to open a bank account or bank accounts with such banks, bankers, and/or trust companies as they or each of them shall determine, and to deposit therein to the credit of the Corporation from time to time any and all monies and checks of the Corporation; and

Resolved, that the banks, bankers, and/or trust companies so designated as depositaries of the Corporation be, and they hereby are, severally authorized to honor and pay all checks, drafts, and other orders for the payment of money drawn upon such account or accounts (including checks, drafts, or other orders of one or both of the persons making, signing, or drawing them) made, signed or drawn by the following persons: Charles W. Hooker or William U. Gardner."

It was also *"Resolved,* that The Greenwich Savings Bank of 1356 Broadway and 985 Sixth Avenue, Borough of Manhattan, City of New York, is hereby designated as depositary of funds of this corporation and is authorized to honor drafts and orders for the payment and withdrawal of moneys therefrom made in the name of this corporation and signed by President, William U. Gardner, or Secretary-Treasurer, Charles W. Hooker.

"And it is Further *Resolved* that the foregoing authority shall continue until written notice of revocation of this Resolution shall be received by The Greenwich Savings Bank.

"And it is Further *Resolved* that said The Greenwich Savings Bank is authorized to accept the certificate of the Secretary of this corporation as evidence of the names and signatures of the persons at any time authorized to act pursuant to this Resolution."

It was voted, "That the sum of one dollar per member of the Association be paid to *Cancer Research* as of March 1, 1947."

It was voted, "That the sum of $150 be appropriated to the Acting Secretary-Treasurer for secretarial assistance."

It was voted, "That the publication of the minutes and of the scientific proceedings of the meeting be authorized and that the expenses incurred be paid with funds of the Association."

It was voted, "That practice of publication in alternate years of the By-Laws, and the list of officers and members be resumed, the cost to be met with funds of the Association."

It was agreed to defer action on the exemption of members of the armed forces from payment of dues.

The question of amending the By-Laws to state the terms of office of the officers and to specify the qualifications for election to membership was discussed without action being taken. It was agreed that the question of qualifications for membership be studied by the Membership Committee.

It was voted that, "The Association plan to meet in conjunction with the meeting of the Federation of American Societies for Experimental Biology in the early part of the week."

It was agreed that the Chairman of the Board investigate the possibility of the Association's affiliating with the Federation and report at the next meeting of the Board.

The meeting adjourned at 1:00 a. m., March 12, 1946.

WILLIAM U. GARDNER, *Chairman,*
Board of Directors

CHARLES W. HOOKER,
Acting Secretary

[1] The following committee has since been appointed: E. V. Cowdry, *Chairman,* J. J. Bittner, C. P. Rhoads, and L. A. Scheele.

American Association for Cancer Research, Inc.*

By-Laws

Article I

Section 1. Members. There shall be eight classes of members as follows:

(a) Donors—who shall give to the Corporation the sum of $1,000 or more each. Donors shall be members for life without dues.

(b) Life Members—who shall give to the Corporation the sum of $100. Life members shall be members for life without dues.

(c) Patrons—who shall pay dues to the Corporation of $50 per annum.

(d) Sustaining Members—who shall pay dues to the Corporation of $25 per annum.

(e) Contributing Members—who shall pay dues to the Corporation of $10 per annum.

(f) Active Members—who shall pay dues to the Corporation of $3.00 per annum.

(g) Honorary Members—who need not pay dues to the Corporation.

(h) Emeritus Members—who have attained the age of 65 years, have been members for ten years or more, and who upon application may be exempt from dues.

All persons who, on the date of incorporation of the Corporation, were active members in good standing of the American Association for Cancer Research, an unincorporated association, shall become Active Members of the Corporation as of such date.

All persons who, on the date of incorporation of the Corporation, were Honorary Members of said American Association for Cancer Research shall become Honorary Members of the Corporation as of such date, without payment of dues.

Donors, Life Members, Patrons, Sustaining Members, Contributing Members, and Active Members shall have equal privileges of membership and each shall be entitled to one vote at all meetings of members.

Section 2. Election of Members. The Board of Directors at any time, and from time to time, may elect to membership such persons as they consider eligible.

Section 3. Meetings of Members.

(a) The annual meeting of members shall be held at such time and place, within or without the State of New York, as may be designated in the notice of the meeting.

(b) Special meetings of members may be called by the President or, in his absence or disability, by the Vice-President, only upon (a) the request of the Board of Directors or (b) the request of thirty or more members. Special meetings shall be held at such time and place within or without the State of New York as may be designated in the notice of the meeting.

(c) Notice of each meeting of members, whether annual or special, shall be printed or written, signed by an executive officer, and mailed to each member at his address as it appears upon the books or records of the Corporation not less than ten days nor more than forty days prior to the date of the meeting, and the notice of each special meeting shall state the purpose or purposes for which it is to be held.

(d) A quorum of members shall consist of not less than one-third of the total number of members; provided, however, that if there shall be twenty-seven or more members of the Corporation, a quorum shall consist of nine.

Section 4. Resignations. Resignations of members shall be in writing addressed to the Board of Directors, but no resignation shall be accepted or take effect if the member presenting it shall be indebted to the Corporation.

Section 5. Expulsion. Any member who fails or neglects to pay his dues, or whose conduct shall in the opinion of the Board of Directors be prejudicial to the welfare of the Corporation, may be dropped from membership by the Board of Directors; provided, however, that notice in writing shall be given to such member of the action contemplated and of the grounds therefor at least 15 days previous to the date for the proposed expulsion of such member, and that such member shall be given an opportunity to present in written form and/or by personal appearance before the Board of Directors a defense of the act or acts upon which the proposed expulsion is based.

Section 6. Transfers of Membership. Memberships may be transferred by the Executive Committee from one class to another because of changes in the sum paid annually.

Article II

Section 1. The Board of Directors. The number of directors shall be twelve, who shall be members and who shall divide themselves into three classes. The first class shall serve until the first annual meeting of members, the second class shall serve until the second annual meeting of members, and the third class shall serve until the third annual meeting of members. Directors shall be elected at each annual meeting of members to succeed the directors whose terms shall have expired, and each director then chosen shall serve for a term of three years and until the election of his successor.

Section 2. Duties of Board of Directors. The Board of Directors shall have the following powers and duties:

(a) To nominate candidates for President, Vice-President, and Secretary-Treasurer of the Corporation.

* Incorporated in the State of New York, April 1940. A copy of the Certificate of Incorporation was published in *Cancer Research*, vol. 1, page 72, 1941.

(b) To fill vacancies that may from time to time occur among the officers.

(c) To direct and supervise the activities of the Corporation, its representatives, and employees.

(d) To appoint such committees, standing and special, as may be necessary or desirable to carry on the work of the Corporation.

(e) To prepare or cause to be prepared and to approve annually a budget for the ensuing fiscal year.

(f) To supervise, either directly or through a duly appointed committee, the investment and disbursement of all funds of the Corporation.

(g) To fix the compensation of all representatives and employees of the Corporation.

(h) To present at the annual meeting of members a report as provided by Section 46 of the Membership Corporations Law.

(i) To elect such other officers as may be necessary properly to carry on the work of the Corporation.

(j) To perform such other duties as may be required by law.

Section 3. Annual Meetings. The Board of Directors shall meet immediately after each annual meeting of members in such place, within or without the State of New York, as may be designated in the notice of the meeting.

Section 4. Special Meetings. Special meetings of the Board of Directors may be called by the President or, in his absence or disability, by the Vice-President, and shall be called by him at the request of any two members of the Board of Directors. Special meetings may be held at such time or place, within or without the State of New York, as may be designated in the notice of the meeting. Notice of special meetings shall be given by mail, telephone, telegram, or personally, and shall be so given at least four days before the date of the meeting.

Section 5. Quorum. A quorum of the Board of Directors shall consist of five of its members.

Section 6. Vacancies. Any vacancy or vacancies in the Board of Directors however caused may be filled by a majority of the remaining members of the Board of Directors then in office, though a majority of such remaining members do not constitute a quorum. The director chosen to fill such a vacancy shall hold office only for the unexpired portion, if any, of the term of the director whose office shall have become vacant.

Article III

Section 1. Officers. The officers of the Corporation shall be a President, a Vice-President, and a Secretary-Treasurer, selected from the Board of Directors. The officers shall be elected by the members either from the candidates nominated by the Board of Directors or from candidates nominated by the members. Each officer shall hold office until the next annual meeting of the members and until his successor shall have been elected and shall have qualified.

The Board of Directors may appoint other officers, including an additional Vice-President and an Assistant Secretary-Treasurer to serve for such terms and perform such duties as the Board of Directors may prescribe.

Section 2. Duties of Officers.

President. The President shall be the chief executive of the Corporation and shall preside at all meetings of the Board of Directors.

Vice-President. The Vice-President, in the absence or during the disability of the President, shall have all the powers and perform all the duties of the President.

Secretary-Treasurer. The Secretary-Treasurer shall have the care and custody of all funds and securities and valuable documents belonging to the Corporation. The Secretary-Treasurer shall deposit the funds of the Corporation to its credit in such banks, trust companies, or depositaries as the Board of Directors, or the Committee appointed by the Board of Directors to supervise the investment and disbursement of the funds of the Corporation, may designate. The Secretary-Treasurer shall sign all checks and drafts in the name of the Corporation. The Secretary-Treasurer shall keep full books of account of the Corporation and shall render to the Board of Directors from time to time at its request, and annually to the members, a full statement in regard to its funds.

The Secretary-Treasurer shall keep all minutes and proceedings of the members and of the Board of Directors in books kept for that purpose. He shall give notice of all meetings of the members and of the Board of Directors. He shall have the custody of the seal of the Corporation and shall affix the same when authorized to do so by the Board of Directors.

Article IV

General

Section 1. Fiscal Year. The fiscal year of the Corporation shall begin on the first day of January in each year and shall end on the following 31st day of December.

Section 2. Dues. Dues shall be payable in advance on or before the first day of March, in each year.

Section 3. Local Work. Branches of the Corporation may be formed in the name of the Corporation in such areas as may be approved by the Board of Directors, to carry on work in conjunction with the Corporation under the direction and subject to the approval of the Board of Directors of the Corporation.

Section 4. Seal. The seal of the Corporation shall be circular in form with the words, "American Association for Cancer Research, Inc." on the circumference and the following words in the center:

Corporate Seal 1940 New York.

Section 5. Order of Business. At all regular meetings of members and of the Board of Directors, the order of business shall be as follows:

1. Roll call.
2. Reading of minutes.
3. Reports of officers.
4. Reports of standing committees.
5. Reports of special committees.
6. Reports of other representatives of the Corporation.

7. Unfinished business.
7. New business.
9. Adjournment.

At every annual meeting of members, the Directors, after the reading of the minutes, shall submit a report as required by Section 46 of the Membership Corporations Law.

Section 6. Execution of Instruments. All formal agreements shall be signed by the President or the Vice-President or the Secretary-Treasurer unless otherwise ordered by the Board of Directors.

ARTICLE V

Section 1. Amendments to By-Laws. These By-Laws may be amended, added to, or repealed without notice at any annual meeting or with notice at any special meeting of members by a two-thirds vote of the members present or represented by proxy, or without notice at any annual meeting or with notice at any special meeting of the Board of Directors by a two-thirds vote of the Directors present, as the case may be. Any amendment made by the Board of Directors shall be reported to the members at the next annual meeting.

American Association for Cancer Research, Inc.

List of Members

1946

A

ABELS, JULES C., M.D., Memorial Hospital, York Avenue at 68th Street, New York 21, N. Y.

ACKERMAN, LAUREN V., M.D., Ellis Fischel State Cancer Hospital, Highway 40 and N. Garth Avenue, Columbia, Mo.

ADAIR, FRANK E., Sc.D., M.D., 75 E. 71st Street, New York, N. Y.

ALBERT, SAMUEL, M.D., McGill University, Montreal 2, Quebec, Canada.

ALGIRE, GLENN HORNER, M.D., National Cancer Institute, Bethesda 14, Md.

ANDERSON, RUDOLPH J., Ph.D., 101 Cottage Street, New Haven, Conn.

ANDERVONT, HOWARD B., Sc.D., National Cancer Institute, Bethesda 14, Md.

ANGRIST, ALFRED, B.S., Queens General Hospital, 161st Street and 82nd Drive, Jamaica, N. Y.

ARONS, ISIDORE, M.D., 57 West 57th Street, New York, N. Y.

ASH, COL. J. E., M.D., Army Institute of Pathology, Washington 25, D. C.

AUB, JOSEPH C., M.D., Massachusetts General Hospital, Boston, Mass.

AUGER, CARLETON, M.D., Laval University, Quebec, Canada.

B

BAGG, HALSEY J., Ph.D., Bagg Research Laboratory, Yorktown Heights, Westchester Co., N. Y.

BAKER, ABE B., M.D., 19 Millard Hall, University of Minnesota, Minneapolis 14, Minn.

BALL, HOWARD A., M.D., 233 A Street, San Diego 1, Calif.

BALL, ZELDA B., B.S., Northwestern University, 303 E. Chicago Avenue, Chicago 11, Ill.

BALLANTYNE, ELLIOT N., M.D., St. Joseph's Hospital, 316 John Street S., Hamilton, Ontario.

BARNES, W. A., M.D., New York Hospital, 525 East 68th Street, New York 21, N. Y.

BARNUM, CYRUS P., Ph.D., University of Minnesota Medical School, Minneapolis 14, Minn.

BARRETT, MORRIS K., M.D., National Cancer Institute, Bethesda 14, Md.

BARRON, MOSES, M.D., 1127 Medical Arts Building, Minneapolis 2, Minn.

BARTFELD, HARRY, M.D., New York Post-Graduate Medical School and Hospital, 303 East 20th Street, New York, N. Y.

BASS, ALLAN D., M.D., University of Syracuse College of Medicine, Syracuse, N. Y.

BAUMANN, CARL A., Ph.D., Biochemistry Building, University of Wisconsin, Madison 6, Wis.

BAYNE-JONES, STANHOPE, M.D., The Jane Coffin Childs Memorial Fund for Medical Research, 333 Cedar Street, New Haven 11, Conn.

BEARD, HOWARD H., Ph.D., The Chicago Medical School, 710 South Wolcott Avenue, Chicago, Ill.

BEARD, JOSEPH W., M.D., Duke University School of Medicine, Durham, N. C.

BEHAN, RICHARD J., M.D., 6082 Jenkins Arcade, Pittsburgh 22, Pa.

BELKIN, MORRIS, Ph.D., Medical College of South Carolina, Charleston 16, S. C.

BELL, ELEXIOUS T., M.D., University of Minnesota Medical School, Minneapolis 14, Minn.

BENNETT, MARY A., Ph.D., Lankenau Hospital Research Institute, Corinthian and Girard Aves., Philadelphia 30, Pa.

BERDEZ, GEORGE L., M.D., St. Mary's Hospital, Fifth Avenue E., and Third Street, Duluth 5, Minn.

BERGMANN, WERNER, Ph.D., 94 Cottage Street, New Haven, Conn.

BERRY, GEORGE PACKER, M.D., University of Rochester School of Medicine and Dentistry, 260 Crittenden Boulevard, Rochester 7, N. Y.

BIESELE, JOHN J., Ph.D., Sloan-Kettering Institute for Cancer Research, 444 East 68th Street, New York 21, N. Y.

BISCHOFF, FRITZ, Ph.D., Santa Barbara Cottage Hospital, Santa Barbara, Calif.

BISHOP, EVERETT L., M.D., 204 Medical Arts Building, 384 Peachtree Street N.E., Atlanta, Ga.

BITTNER, JOHN J., Ph.D., University of Minnesota Medical School, Minneapolis 14, Minn.

BLADY, JOHN V., M.D., Medical Tower, 255 South 17th Street, Philadelphia 3, Pa.

BLEYER, LEO F., M.D., St. Francis Hospital, 355 Ridge Avenue, Evanston, Ill.

BLOOR, WALTER R., Ph.D., University of Rochester School of Medicine and Dentistry, 260 Crittenden Boulevard, Rochester 7, N. Y.

BLUM, HAROLD F., Ph.D., Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md.

BLUMENFELD, CHARLES M., M.D., 1433 41st Street, Sacramento 16, Calif.

BLUMENTHAL, HERMAN T., Ph.D., Address unknown.

BOTHE, ALBERT E., M.D., Sc.D., 255 South 17th Street, Philadelphia 3, Pa.

BOUTWELL, R. K., Ph.D., McArdle Memorial Laboratory, University of Wisconsin, Madison 6, Wis.

BRANCH, CHARLES F., M.D., The Children's Hospital, 300 Longwood Avenue, Boston 15, Mass.

BRESLICH, PAUL, M.D., Northwest Clinic, Minot, N. D.

BRIGGS, ROBERT W., Ph.D., Lankenau Hospital Research Institute, Girard and Corinthian Avenues, Philadelphia 30, Pa.

BROWN, ROBERT L., M.D., Winship Clinic, Emory University Hospital, Emory University, Ga.

BRUES, AUSTIN M., M.D., University of Chicago, Chicago 37, Ill.

BRUNSCHWIG, ALEXANDER, M.D., University of Chicago, 950 East 59th Street, Chicago 37, Ill.

BRYAN, W. RAY, Ph.D., National Cancer Institute, Bethesda 14, Md.

BUCHWALD, KENNETH W., A.M., New York State Institute for the Study of Malignant Diseases, 633 N. Oak St., Buffalo 3, N. Y.

BUGHER, JOHN C., M.D., c/o Yellow Fever Research Institute, Lagos, Nigeria.

BUNTING, CHARLES H., M.D., 139 Armory St., Hamden 11, Conn.

BURACK, ETHEL, Ph.D., 500 Park Avenue, Albany, N. Y.

BURK, DEAN, Ph.D., National Cancer Institute, Bethesda 14, Md.

BURKE, EUGENE M., New York State Institute for the Study of Malignant Diseases, 663 N. Oak St., Buffalo 3, N. Y.

BURMESTER, B. R., Ph.D., Regional Poultry Research Laboratory, East Lansing, Mich.

BURN, CASPAR G., M.D., 726 Ocean Avenue, Brooklyn 26, N. Y.

BURNAM, CURTIS F., M.D., Howard A. Kelly Hospital, 1418 Eutaw Place, Baltimore 17, Md.

BURNS, EDWARD L., M.D., Mercy Hospital, Madison at 23rd Street, Toledo 2, Ohio.
BURROWS, MONTROSE T., M.D., 201 N. El Molino Ave., Pasadena 4, Calif.

C

CANTAROW, ABRAHAM, M. D., Jefferson Medical College, 1025 Walnut Street, Philadelphia 7, Pa.
CARRUTHERS, CHRISTOPHER, Ph.D., Barnard Free Skin and Cancer Hospital, 3427 Washington Boulevard, St. Louis 3, Mo.
CASEY, ALBERT E., M.D., Baptist Hospitals, Birmingham, Ala.
CHAMBERS, ROBERT, Ph.D., Washington Square College of Arts and Science, Washington Square, New York 3, N. Y.
CHAMBERS, WILLIAM H., Ph.D., Cornell University Medical College, 1300 York Avenue, New York 21, N. Y.
CHILDS, S. WINSTON, 1 Wall Street, New York, N. Y.
CHILDS, STARLING W., 1 Wall Street, New York, N. Y.
CHRISTEN, HENRIETTA C., M.D., 44 Sage Avenue, Buffalo, N. Y.
CHRISTIAN, MRS. GEORGE C., 2303 Third Avenue, Minneapolis, Minn.
CHRISTY, CHRIST JOHN, M.D., New York State Institute for the Study of Malignant Diseases, 663 N. Oak St., Buffalo 3, N. Y.
CLARKE, B. EARLE, M.D., Rhode Island Hospital, Providence 2, R. I.
CLAUDE, ALBERT, M.D., Rockefeller Institute for Medical Research, 66th Street and York Avenue, New York 21, N. Y.
CLAWSON, BENJAMIN J., Ph.D., M.D., 500 S. E. Delaware Street, Minneapolis, Minn.
CLINE, JOSEPH K., Ph.D., Hillman Hospital, Birmingham 3, Ala.
CLOUDMAN, ARTHUR M., Ph. D., Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Me.
CLOWES, GEORGE H. A., Ph.D., Sc.D., Eli Lilly and Company, Indianapolis 6, Ind.
COCA, ARTHUR F., M.D., 425 Grant Avenue, Oradell, N. J.
COHEN, MORTIMER, M.D., 5615 Bartlett Street, Pittsburgh 17, Pa.
COHEN, PHILIP P., Ph.D., M.D., Service Memorial Institute, University of Wisconsin Medical School, Madison, Wis.
COLE, R. K., Ph.D., Cornell University, Ithaca, N. Y.
COLEY, BRADLEY L., M.D., Memorial Hospital, 444 East 68th Street, New York 21, N. Y.
COLLIP, JAMES B., Ph.D., Sc.D., M.D., McGill University Faculty of Medicine, 3640 University Street, Montreal, Quebec, Canada.
COMAN, DALE R., M.D., University of Pennsylvania School of Medicine, Philadelphia, Pa.
COOMBE, REGINALD G., A.B., 305 Lake Avenue, Greenwich, Conn.
COOPER, ZOLA K., Ph.D., Barnard Free Skin and Cancer Hospital, Washington and Theresa Avenues, St. Louis 3, Mo.
COSTELLO, CYRIL J., M.D., St. Louis City Hospital, 1515 Lafayette Avenue, St. Louis 4, Mo.
COWDRY, EDMUND V., Ph.D., Barnard Free Skin and Cancer Hospital, Washington and Theresa Avenues, St. Louis 3, Mo.
COX, ALVIN J., JR., M.D., Stanford University School of Medicine, 2398 Sacramento Street, San Francisco, Calif.
CRAVER, LLOYD F., M.D., 772 Madison Ave., New York 21, N. Y.
CREECH, HUGH J., Ph.D., Lankenau Hospital Research Institute, Girard and Corinthian Avenues, Philadelphia 30, Pa.
CREEVY, CHARLES DONALD, Ph.D., M.D., 305 Medical Arts Building, Minneapolis 2, Minn.
CROSSLAND, RUTH SNIDER, Ph.D., University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester 7, N. Y.
CROWELL, BOWMAN C., M.D., American College of Surgeons, 40 East Erie Street, Chicago, Ill.
CRUZ, JUAN Z. STA., M.D., St. Lukes Hospital, Manila, P. I.
CULLEN, THOMAS S., M.D., Sc.D., 20 East Eager Street, Baltimore 2, Md.
CUTLER, MAX, M.D., 430 North Michigan Avenue, Chicago 11, Ill.

D

DALTON, ALBERT J., Ph.D., National Cancer Institute, Bethesda 14, Md.
DANIEL, GEORGE E., Sc.D., National Cancer Institute, Bethesda 14, Md.
DAVENPORT, HAROLD A., M.D., Northwestern University Medical School, 303 East Chicago Avenue, Chicago 11, Ill.
DAVIS, HARRY A., M.D., College of Medical Evangelists, Boyle & Michigan Avenues, Los Angeles 33, Calif.
DEADMAN, WILLIAM J., M.D., Hamilton General Hospital, Barton Street E., Hamilton, Ontario.
DERINGER, MARGARET K., Ph.D., National Cancer Institute, Bethesda 14, Md.
DEVITA, JOSEPH, V.M.D., 724 Whitney Avenue, New Haven 11, Conn.
DISCHE, ZACHARIUS, M.D., College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York 32, N. Y.
DOBRINER, KONRAD, M.D., Memorial Hospital, York Avenue at 68th Street, New York 21, N. Y.
DOISY, EDWARD A., Ph. D., Sc.D., St. Louis University School of Medicine, 1402 South Grand Blvd., St. Louis 4, Mo.
DONNER, WILLIAM H., Donner Foundation, Inc., Land Title Building, Philadelphia 10, Pa.
DORFMAN, RALPH I., Ph.D., Western Reserve University School of Medicine, 2085 Adelbert Road, Cleveland 6, Ohio.
DORRANCE, GEORGE M., M.D., 2101 Spruce Street, Philadelphia 3, Pa.
DOUGHERTY, THOMAS F., Ph.D., Yale University School of Medicine, 333 Cedar Street, New Haven 11, Conn.
DOWDY, ANDREW H., M.D., University of Rochester School of Medicine and Dentistry, 260 Crittenden Boulevard, Rochester 7, N. Y.
DOWLING, ALEXANDER S., M.D., 134 East First Street, Corning, N. Y.
DRABKIN, DAVID L., M.D., University of Pennsylvania School of Medicine, Philadelphia 4, Pa.
DUBILIER, BENJAMIN, M.D., U. S. Naval Hospital, Brooklyn, N. Y.
DUFRESNE, ORIGÈNE, Institut du Radium, 4120 Ontario Street, E., Montreal, Canada.
DUNLAP, CHARLES E., M.D., Tulane Medical School, New Orleans, La.
DUNN, THELMA B., M.D., National Cancer Institute, Bethesda 14, Md.
DURAN-REYNALS, FRANCISCO, M.D., Yale University School of Medicine, 333 Cedar Street, New Haven 11, Conn.
DUVIGNEAUD, VINCENT, Ph.D., Cornell University Medical College, 1300 York Avenue, New York 21, N. Y.
DYER, HELEN M., Ph.D., National Cancer Institute, Bethesda 14, Md.

E

EARLE, WILTON R., Ph.D., National Cancer Institute, Bethesda 14, Md.
EBERHARD, THEODORE P., M.D., Jefferson Hospital, 10th and Sanson Street, Philadelphia 7, Pa.
EDWARDS, JESSE E., M.D., Section of Pathological Anatomy, Mayo Clinic Rochester, Minn.
EGGERS, CARL, M.D., 850 Park Avenue, New York 21, N. Y.
EGGERS, HAROLD E., M.D., University of Nebraska, College of Medicine, 42nd and Dewey Avenue, Omaha 5, Nebr.
EISEN, MILTON J., M.D., College of Physicians and Surgeons, 630 West 168th Street, New York 32, N. Y.
EISENHARDT, LOUISE, M.D., Yale University School of Medicine. 333 Cedar Street, New Haven 11, Conn.
ELLER, JOSEPH J., M.D., Harvey Building, West Palm Beach, Fla.
ELSBERG, CHARLES A., M.D., 168th Street and Ft. Washington Avenue, New York 32, N. Y.
ELTON, W. NORMAN, M.D., Address unknown.
ENGEL, LEWIS L., Ph.D., Huntington Laboratories, Massachusetts General Hospital, Boston 14, Mass.

ENGLE, EARL T., Ph.D., College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York 32, N. Y.
ERDMANN, JOHN F., M.D., 122 East 70th Street, New York 21, N. Y.
ERF, LOWELL A., M.D., Garden Court Plaza, Pine and 47th Street, Philadelphia, Pa.
ESCHELMAN, KARL F., D.D.S., M.D., 351 Linwood Avenue, Buffalo 9, New York.
EVANS, TITUS CARR, Ph.D., College of Physicians and Surgeons, 630 West 168th Street, New York 32, N. Y.
EVANS, VIRGINIA JOHN, Sc.D.,National Cancer Institute, Bethesda 14, Md.

F

FAILLA, GIOACCHINO, D.Sc., College of Physicians and Surgeons, 630 West 168th Street, New York 32, N. Y.
FALK, K. GEORGE, Ph.D., 40 East 66th Street, New York, N. Y.
FARROW, JOSEPH H., M.D., Address unknown.
FEKETE, ELIZABETH, A.M., Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Me.
FETTERMAN, GEORGE H., M.D., Walnut Street, Castle Shannon, Pittsburgh, Pa.
FIESER, LOUIS F., Ph.D., Converse Memorial Laboratory, Harvard University, Cambridge, Mass.
FIGGE, FRANK H. J., Ph.D., University of Maryland School of Medicine, Lombard and Greene Sts., Baltimore 1, Md.
FIROR, WARFIELD M., M.D., Johns Hopkins Hospital, 601 N. Broadway, Baltimore 5, Md.
FLEMING, R. M., M.D., 444 Ingraham Building, Miami, Fla.
FLORY, CURTIS M., Ph.D., M.D., Cornell University Medical School, 1300 York Avenue, New York 21, N. Y.
FOGG, LLOYD C., Ph.D., Boston University School of Medicine, Boston, Mass.
FOOT, NATHAN CHANDLER, M.D., 340 East 72nd Street, New York 21, N. Y.
FOOTE, FRANK W., JR., M.D., Memorial Hospital, York Avenue at 68th Street, New York 21, N. Y.
FRANING, EDWARD C. G., M.D., Bank of Galesburg Building, Galesburg, Ill.
FRANKS, WILLIAM R., M.D., Banting Institute, 100 College Street, Toronto, Ontario, Canada.
FRAZELL, EDGAR LEONARD, M.D., 737 Park Avenue, New York 21, N. Y.
FRIEDGOOD, HARRY B., M.D., 2943 Queensbury Drive, Los Angeles 34, Calif.
FRIEDMAN, HARRY F., M.D., 270 Commonwealth Avenue, Boston, Mass.
FRIEDMAN, MILTON, M.D., 153 East 72nd Street, New York, N. Y.
FURTH, JACOB, M.D., Cornell University Medical College, 1300 York Avenue, New York 21, N. Y.

G

GALLO, JAMES S., M.D., 594 Broadway, Paterson 4, N. J.
GARAI, FRANK, M.D., Manhattan Eye, Ear and Throat Hospital, 210 East 64th Street, New York, N. Y.
GARDNER, WILLIAM U., Ph.D., Yale University School of Medicine, 333 Cedar St., New Haven 11, Conn.
GATES, OLIVE, M.D., 25 Shattuck Street, Boston, Mass.
GENDREAU, JOSEPH ERNEST, M.D., Institut du Radium, 4120 Ontario Street, E., Montreal, Quebec, Canada.
GEY, GEORGE O., M.D., Laboratory of Cellular Pathology, 531 Dispensary Building, Johns Hopkins Medical School, Baltimore, Md.
GOLDBLATT, HARRY, M.D., Western Reserve University, 2085 Adelbert Road, Cleveland, Ohio.
GOLDFEDER, ANNA, Sc.D., M.A.C., New York University, College of Medicine, 477 First Avenue, New York 16, N. Y.
GOLDSMITH, ELI D., Ph.D., New York University, College of Dentistry, 447 First Avenue, New York 16, N. Y.
GOLTZ, HILDA LEE, 663 N. Oak Street, Buffalo 3, N. Y.
GONZALEZ, ABRAHAM AYALA, M.D., Plaza de la Republica No. 46, Mexico City, Mexico.
GOPAL-AYENGAR, A. R., Ph.D., Barnard Free Skin and Cancer Hospital, Washington and Theresa Avenues, St. Louis 3, Mo.
GOTTSCHALK, RAYMOND G., M.D., 3 Quai du Barbou, Liége, Belgium.
GRADY, HUGH G., M.D., 4400 Cedar Lane, Drexel Hill, Pa.
GRAUER, ROBERT C., M.D., Allegheny General Hospital, 320 East North Avenue, Pittsburgh, Pa.
GRAY, SAMUEL H., M.D., Jewish Hospital, 216 South Kingshighway Boulevard, St. Louis, Mo.
GREEN, ELIZABETH UFFORD, Ph.D., Lankenau Hospital Research Institute, Girard and Corinthian Avenues, Philadelphia 30, Pa.
GREEN, ROBERT G., M.D., University of Minnesota, Minneapolis 14, Minn.
GREENE, HARRY S. N., M.D., Yale University School of Medicine, 333 Cedar Street, New Haven 11, Conn.
GREENSTEIN, JESSE P., Ph.D., National Cancer Institute, Bethesda 14, Md.
GRISWOLD, MATTHEW H., M.D., Dr. P.H., Connecticut State Department of Health, 165 Capitol Avenue, Hartford, Conn.
GUIMARAES, UGO PINHEIRO, M.D., r. Urugayana 104, 5° andar, Rio de Janeiro, Brazil, S. A.
GUZMAN, GONZALEZ, M.D., Calle Ramon Guzman #34, Mexico, D. F.
GUZMAN, LEONARDO, M.D., National Radiation Institute, Santiago, Chile, S. A.

H

HAAGENSEN, CUSHMAN D., M.D., College of Physicians and Surgeons, Columbia University, New York 32, N. Y.
HALPERT, BÉLA, M.D., University of Oklahoma School of Medicine, 800 Northeast Thirteenth Street, Oklahoma City 4, Okla.
HAMILTON, JAMES B., Ph.D., Long Island College of Medicine, 350 Henry Street, Brooklyn 2, N. Y.
HARRIS, PAUL, M.D., Eli Lilly and Company, 740 South Alabama Street, Indianapolis 6, Ind.
HARRISON, ROSS G., Ph.D., Sc.D., M.D., 142 Huntington Street, New Haven, Conn.
HASTINGS, A. BAIRD, Ph.D., Sc.D., Harvard Medical School, 25 Shattuck Street, Boston 15, Mass.
HASTINGS, WILLARD S., M.D., Jeanes Hospital, Barnes and Hartel Streets, Philadelphia 11, Pa.
HAUSER, HARRY, M.D., Western Reserve University Medical School, 3395 Scranton Road, Cleveland 9, Ohio.
HAVEN, FRANCES L., Ph.D., University of Rochester School of Medicine and Dentistry, 260 Crittenden Boulevard, Rochester 7, N. Y.
HAYMAKER, WEBB, M.D., Army Institute of Pathology, Washington 25, D. C.
HAYTHORN, SAMUEL R., M.D., Wm. H. Singer Memorial Laboratory, 320 East North Avenue, N.S., Pittsburgh, Pa.
HEBBEL, ROBERT, M.D., University of Minnesota Medical School, Minneapolis 14, Minn.
HEILMAN, FORDYCE R., M.D., Mayo Foundaton, Rochester, Minn.
HEIMAN, HELEN I., M.D., 15 West 81st Street, New York, N. Y.
HEIMAN, JACOB, M.D., College of Physicians and Surgeons, 630 West 168th Street, New York 32, N. Y.
HEKTOEN, LUDVIG, M.D., Sc.D., Chicago Tumor Institute, 21 West Elm Street, Chicago 10, Ill.
HELLWIG, CHRISTIAN A., M.D., St. Francis Hospital, 928 North Emporia Avenue, Wichita, Kans.
HELMBOLD, THEODORE R., M.D., South Side Hospital, Pittsburgh 3, Pa.
HELMER, OSCAR M., Ph.D., Eli Lilly and Company, Indianapolis, Ind.
HELWIG, FERDINAND C., M.D., St. Luke's Hospital, 44th and Mill Creek Parkway, Kansas City 2, Mo.
HENGERER, AUGUSTUS W., M.D., 333 Linwood Avenue, Buffalo, N. Y.
HENSHAW, PAUL S., Ph.D., 105 West Malta Road, Oak Ridge, Tenn.

HERGER, CHARLES C., M.D., New York State Institute for the Study of Malignant Diseases, 663 N. Oak Street, Buffalo 3, N. Y.

HERLY, LOUIS, M.D., College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York 32, N. Y.

HERTZLER, ARTHUR E., Ph.D., M.D., 327 Chestnut Street, Halstead, Kans.

HESSELBACH, MARIE L., National Cancer Institute, Bethesda 14, Md.

HESTON, WALTER E., Ph.D., National Cancer Institute, Bethesda 14, Md.

HODES, PHILIP J., M.D., Sc.D., 3400 Spruce Street, Philadelphia 4, Pa.

HOFFMAN, JOSEPH G., Ph.D., Address unknown.

HOFFMAN, WILLIAM J., M.D., 153 East 72nd Street, New York 21, N. Y.

HOLLANDER, LESTER, M.D., 631 Jenkins Building, Pittsburgh, Pa.

HOLMES, MISS HARRIET F., Selborne, South Batavia Road, Batavia, Ill.

HOMBERGER, FREDDY, M.D., Memorial Hospital, York Avenue at 68th Street, New York 21, N. Y.

HOOKER, CHARLES WRIGHT; Ph.D., Yale University School of Medicine, New Haven 11, Conn.

HORN, ROBERT C., M.D., Hospital of the University of Pennsylvania, Philadelphia 4, Pa.

HOSTER, HERMAN A., M.D., Kinsman Hall, Ohio State University, Columbus, Ohio.

HOWE, MARTHA ELIZABETH, M.D., 901 Lexington Avenue, New York, N. Y.

HUDSON, LEONA, M.S., New York State Institute for the Study of Malignant Diseases, 663 N. Oak Street, Buffalo 3, N. Y.

HUEPER, WILHELM C., M.D., 150 Madison Road, Scarsdale, N. Y.

HUGGINS, CHARLES, M.D., University of Chicago, Chicago 37, Ill.

HUSEBY, ROBERT A., M.D., University of Minnesota, Minneapolis 14, Minn.

I

IKEDA, KANO, M.D., Charles T. Miller Hospital, 125 West College Avenue, St. Paul, Minn.

J

JACKSON, ELIZABETH B., 77 Marlboro Street, Boston, Mass.

JACOBS, WILLIAM F., M.D., 408 Richmond Avenue, Buffalo, N. Y.

JACOBSEN, VICTOR C., M.D., 51 First Street, W., Troy, N. Y.

JESSUP, DAVID S. D., M.D., 411 West 114th Street, New York 25, N. Y.

JONES, BENJAMIN F., M.D., 5 F Garden Apartments, Baltimore 10, Md.

JONES, E. ELIZABETH, Ph.D., Wellesley College, Wellesley 81, Mass.

JONES, HARDIN B., Ph.D., University of California, 1106 Oxford Street, Berkeley, Calif.

JONES, R. NORMAN, Ph.D., Queen's University, Kingston, Ontario, Canada.

JORSTAD, LOUIS H., M.D., 411 Beaumont Medical Building, St. Louis 8, Mo.

JOSEPH, BARNET, M.D., 340 East 57th Street, New York, N. Y.

K

KAEMPFFERT, WALDEMAR, Ph.D., 325 West End Avenue, New York, N. Y.

KAHLSTROM, SAMUEL C., M.D., 6273 Meridian Street, Los Angeles 42, Calif.

KALISS, N., Ph.D., Cornell University Medical College, 1300 York Avenue, New York 21, N. Y.

KAPLAN, HENRY S., M.D., Yale University School of Medicine, New Haven 11, Conn.

KAPLAN, IRA I., M.D., 755 Park Avenue, New York 21, N. Y.

KARSNER, HOWARD T., M.D., Western Reserve University School of Medicine, 2085 Adelbert Road, Cleveland 6, Ohio.

KELLERT, ELLIS, M.D., Ellis Hospital Laboratory, Nott Street and Rosa Road, Schenectady 8, N. Y.

KENNEY, JOHN M., M.D., Memorial Hospital, York Avenue at 68th Street, New York 21, N. Y.

KENSLER, C. J., M.A., Memorial Hospital, York Avenue at 68th Street, New York 21, N. Y.

KIDD, JOHN G., M.D., Cornell University Medical College, 1300 York Avenue, New York 21, N. Y.

KILGORE, ALSON R., M.D., 490 Post Street, San Francisco, Calif.

KIRSCHBAUM, ARTHUR, M.D., Ph.D., University of Minnesota Medical School, Minneapolis 14, Minn.

KLINE, M. BERNERD E., M.D., 422 McArdle Memorial Laboratory, University of Wisconsin, Madison 6, Wis.

KOPAC, M. J., Ph.D., New York University, 14 Washington Place, New York 3, N. Y.

KOUCKY, RUDOLPH W., M.D., St. Mary's Hospital, 2500 S. 6th Street, Minneapolis, Minn.

KRAEMER, WILLIAM H., M.D., 2099 duPont Building, Wilmington 41, Del.

KRAHL, MAURICE E., Ph.D., College of Physicians and Surgeons, 630 West 168th Street, New York 32, N. Y.

KRANTZ, JOHN C., JR., Ph.D., Sc.D., 29 South Greene Street, Baltimore 1, Md.

KREHBIEL, OTTO F., M.D., 116 East 56th Street, New York 22, N. Y.

KRESS, LOUIS C., M.D., 188 Ruskin Road, Eggertsville, N. Y.

KRETSCHMER, HERMAN L., M.D., 122 S. Michigan Avenue, Chicago 3, Ill.

KRUMBHAAR, EDWARD B., M.D., Ph.D., University of Pennsylvania Medical School, 36th and Spruce Streets, Philadelphia, Pa.

KURZROK, RAPHAEL, M.D., Morrisania City Hospital, 1016 Fifth Avenue, New York, N. Y.

L

LAIPPLY, THOMAS C., M.D., Western Reserve University, 2085 Adelbert Road, Cleveland 6, Ohio.

LAMBERT, ROBERT A., M.D., Rockefeller Foundation, 49 West 49th Street, New York, N. Y.

LAN, TIEN HO, Ph.D., University of Rochester School of Medicine and Dentistry, Rochester 7, N. Y.

LARSEN, C. DONALD, Ph.D., National Cancer Institute, Bethesda 14, Md.

LAVAKE, RAY T., M.D., 718 Medical Arts Building, Minneapolis, Minn.

LAW, LLOYD W., Ph.D., Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Me.

LAWRENCE, JOHN H., M.D., Crocker Laboratory, University of California, Berkeley, Calif.

LEACH, JOHN E., M.D., Memorial Hospital, York Avenue and 68th Street, New York 21, N. Y.

LECOMPTE, PHILIP M., M.D., New England Deaconess Hospital, 195 Pilgrim Road, Boston, Mass.

LENZ, MAURICE, M.D., 180 Ft. Washington Avenue, New York 32, N. Y.

LEONARD, VEADER, M.D., 7400 York Road, Baltimore 4, Md.

LEPAGE, G. A., Ph.D., McArdle Memorial Laboratory, University of Wisconsin, Madison 6, Wis.

L'ESPERANCE, ELISE, M.D., New York Infirmary for Women & Children, 2 East 61st Street, New York, N. Y.

LEUCHTENBERGER, MRS. CECELIE, Cancer Research Lab., Mt. Sinai Hospital, Fifth Avenue and 100th Street, New York 29, N. Y.

LEUCHTENBERGER, RUDOLF, M.D., Mount Sinai Hospital, 12 East 97th Street, New York, N. Y.

LEVIN, ISAAC, M.D., 57 West 57th Street, New York, N. Y.

LEVIN, MORTON L., M.D., New York State Health Department, 18 Dove Street, Albany, N. Y.

LEVINE, MICHAEL, Ph.D., Montefiore Hospital, 100 East Gun Hill Road, New York, N. Y.

LEWIS, WARREN H., M.D., Wistar Institute of Anatomy and Biology, 36th Street and Woodland Avenue, Philadelphia, Pa.

LEWISOHN, RICHARD, M.D., 1155 Park Avenue, New York 28, N. Y.

LIPPINCOTT, STUART W., M.D., University of Washington School of Medicine, Seattle, Wash.

LITTAUER, LUCIUS N., 235 Fourth Avenue, New York, N. Y.
LITTLE, CLARENCE C., Sc.D., Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Me.
LOCKWOOD, JOHN S., M.D., College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York 32, N. Y.
LODER, MARGARET M., M.D., Pathological Laboratory, United Hospital, Port Chester, New York.
LOEB, LEO, M.D., Washington University Medical School, 640 South Kingshighway Boulevard, St. Louis 10, Mo.
LONG, WILLIAM BAYARD, M.D., 1192 Park Avenue, New York 28, N. Y.
LORENZ, EGON, Ph.D., National Cancer Institute, Bethesda 14, Md.
LUCKÉ, BALDUIN, M.D., Army Institute of Pathology, Washington, D. C. University of Pennsylvania School of Medicine, 36th and Spruce Streets, Philadelphia, Pa.
LUND, CHARLES C., M.D., 319 Longwood Avenue, Boston 15, Mass.
LUND, HERBERT, M.D., Western Reserve University, Cleveland, Ohio.
LYNCH, CLARA J., Ph.D., Rockefeller Institute for Medical Research, 66th Street and York Avenue, New York 21, N. Y.
LYNCH, KENNETH M., M.D., Medical College of South Carolina, Charleston 16, S. C.

M

MACCARDLE, ROSS C., Ph.D., Washington University School of Dentistry, St. Louis, Mo.
MCCARTNEY, JAMES S., M.D., University of Minnesota Medical School, Minneapolis 14, Minn.
MACCARTY, WILLIAM C., SR., M.D., Mayo Clinic, Rochester, Minn.
MCCAWLEY, ELTON L., Ph.D., Yale University School of Medicine, New Haven 11, Conn.
MACDONALD, ELEANOR J., A.B., Connecticut State Department of Health, 165 Capitol Avenue, Hartford, Conn.
MCDONALD, ELLICE E., M.D., Biochemical Research Foundation, Franklin Institute, Newark, Del.
MCFARLAND, JOSEPH, M.D., University of Pennsylvania, Philadelphia, Pa.
MACFARLANE, CATHARINE, M.D., Women's Medical College, 136 S. 16th Street, Philadelphia 2, Pa.
MACNEAL, WARD J., M.D., Ph.D., New York Post-Graduate Medical School, 303 East Twentieth Street, New York 3, N. Y.
MAHAN, MRS. ARCHIE I., Ph.D., 3824 V Street, S. E., Washington, D. C.
MAHONEY, EARLE B., M.D., Strong Memorial Hospital, 260 Crittenden Boulevard, Rochester 7, N. Y.
MANSON, MELVILLE H., M.D., Ph.D., American Telephone and Telegraph Company, 195 Broadway, New York 7, N. Y.
MARINE, DAVID, M.D., Sc.D., Montefiore Hospital, 150 East Gun Hill Road, New York, N. Y.
MARSHAK, ALFRED, Ph.D., Rockefeller Institute, York Avenue and 66th Street, New York 21, N. Y.
MARTIN, HAYES E., M.D., 737 Park Avenue, New York 21, N. Y.
MATAS, RUDOLPH, M.D., Sc.D., 2255 St. Charles Avenue, New Orleans, La.
MATTICK, WALTER L., M.D., 290 Highland Avenue, Buffalo, N. Y.
MAVER, MARY E., Ph.D., National Cancer Institute, Bethesda 14, Md.
MEADER, RALPH G., Ph.D., The Jane Coffin Childs Fund for Medical Research, 333 Cedar Street, New Haven 11, Conn.
MEDES, GRACE, Ph.D., Lankenau Hospital Research Institute, Girard and Corinthian Avenues, Philadelphia 30, Pa.
MEISSNER, WILLIAM A., M.D., New England Deaconess Hospital, 195 Pilgrim Road, Boston 15, Mass.
MELROY, MALCOLM B., M.D., 1651 Primrose Road, N. W., Washington, D. C.
MENDEL, BRUNO, M.D., Banting Institute, 100 College Street, Toronto, Ontario, Canada.
MENKE, JOHN F., M.D., Stanford University Hospital, Clay and Webster Streets, San Francisco, Calif.
MENKIN, VALY, M.D., Duke University School of Medicine, Durham, N. C.
MENTEN, MAUDE L., M.D., Ph.D., University of Pittsburgh School of Medicine, Bigelow Boulevard, Pittsburgh, Pa.
MEYER, HERBERT WILLY, M.D., 170 East 78th Street, New York 21, N. Y.
MIDER, G. BURROUGHS, M.D., Strong Memorial Hospital, Rochester 7, N. Y.
MILLAN, IGNACIO Y. M., M.D., Cancer Clinic General Hospital, Avenue Veracruz 69, Mexico City, Mexico.
MILLER, ELIZABETH C., Ph.D., McArdle Memorial Laboratory, University of Wisconsin, Madison 6, Wis.
MILLER, JAMES A., Ph.D., McArdle Memorial Laboratory, University of Wisconsin, Madison 6, Wis.
MILLIKEN, SETH M., M.D., 951 Madison Avenue, New York 21, N. Y.
MINOT, GEORGE R., M.D., Sc.D., Thorndike Memorial Laboratory, Boston City Hospital, 818 Harrison Avenue, Boston, Mass.
MIRO-QUESADA, OSCAR, JR., M.D., Paseo Colon 201, Lima, Peru, S. A.
MOHS, FREDERIC E., M.D., State of Wisconsin General Hospital, 1300 University Avenue, Madison, Wis.
MOORE, ROBERT A., Ph.D., M.D., Washington University School of Medicine, Euclid Avenue and Kingshighway, St. Louis 10, Mo.
MORITZ, ALAN R., M.D., Harvard Medical School, 25 Shattuck Street, Boston 15, Mass.
MORRIS, HAROLD P., Ph.D., National Cancer Institute, Bethesda 14, Md.
MORTON, JOHN J., M.D., 108 Sandringham Road, Rochester, N. Y.
MOSHER, HARRIS P., M.D., 127 Front Street, Marblehead, Mass.
MOSS, LEO DAVID, M.D., Olean General Hospital, Olean, N. Y.
MURPHY, EDWIN D., M.D., University of Tennessee, School of Medicine, Memphis 7, Tenn.
MURPHY, GIBBONS W., M.D., Flatiron Building, Asheville, N. C.
MURPHY, JAMES B., M.D., Sc.D., The Rockefeller Institute, 66th Street and York Avenue, New York 21, N. Y.
MURRAY, MARGARET R., Ph.D., College of Physicians and Surgeons, 630 West 168th Street, New York 32, N. Y.
MURRAY, WILLIAM S., Sc.D., New York State Institute for the Study of Malignant Diseases, 663 North Oak Street, Buffalo 3, N. Y.
MYERS, WILLIAM G., Ph.D., M.D., College of Medicine, Ohio State University, Columbus 10, Ohio.

N

NAKAHARA, WARO, M.D., Ph.D., 1141 Mejiro, Tokyo, Japan.
NATHANSON, IRA T., M.D., Massachusetts General Hospital, Boston, Mass.
NELSON, WARREN O., Ph.D., University of Iowa, Iowa City, Iowa.
NETTLESHIP, ANDERSON, M.D., Alexander Blain Hospital, 2201 Jefferson Avenue, East, Detroit, Mich.
NEWELL, ROBERT R., M.D., Stanford University Hospital, Clay and Webster Streets, San Francisco 15, Calif.
NICHOLAS, JOHN S., Ph.D., 170 Cold Spring Street, New Haven, Conn.
NOBLE, JOHN F., M.D., Ancker Hospital, 1783 Eleanor Street, St. Paul 1, Minn.
NORRIS, EDGAR H., M.D., 607 Lakepointe Road, Grosse Pointe, Mich.
NOYES, HELEN M., A.M., Carthage, Ill.

O

OBERHELMAN, HARRY A., M.D., 701 Columbian Avenue, Oak Park, Ill.
O'BRIEN, WILLIAM A., M.D., University of Minnesota, Minneapolis 14, Minn.
OEHLBECK, LUTHER W., M.D., Grace Hospital, Morganton, N. C.
OGDEN, RALPH T., M.D., 179 Allyn Street, Hartford, Conn.

Olch, Isaac Y., M.D., 6022 Wilshire Boulevard, Los Angeles 36, Calif.
Olcott, Charles T., M.D., Cornell University Medical School, 1300 York Avenue, New York 21, N. Y.
Oliver, Clarence P., Ph.D., University of Minnesota, Minneapolis 14, Minn.
Opie, Eugene L., M.D., Sc.D., Rockefeller Institute for Medical Research, 66th Street & York Avenue, New York 21, N. Y.
Ormsby, Oliver S., M.D., 55 East Washington Street, Chicago, Ill.
Oughterson, Ashley Webster, M.D., American Cancer Society, 350 Fifth Avenue, New York 1, N. Y.
Ower, John J., M.D., University of Alberta, Edmonton, Alberta, Canada.

P

Pack, George T., M.D., 139 East 36th Street, New York 16, N. Y.
Papanicolaou, George N., M.D., Cornell University Medical College, 1300 York Avenue, New York 21, N. Y.
Paschkis, Karl E., M.D., Jefferson Medical College, 1025 Walnut Street, Philadelphia 7, Pa.
Pawling, Jesse R., M.D., 205 Trust Company Building, 100 Stone Street, Watertown, N. Y.
Pearce, Louise, M.D., Rockefeller Institute, Princeton, N. J.
Pearson, Bjarne, M.D., University of Vermont, Burlington, Vt.
Pendergrass, Eugene P., M.D., University of Pennsylvania School of Medicine, 3400 Spruce Street, Philadelphia 4, Pa.
Perlman, Robert M., M.D., U. S. Marine Hospital, San Francisco, Calif.
Permar, Howard H., M.D., Mercy Hospital, Pride and Locust Streets, Pittsburgh 19, Pa.
Perry, Isabella H., M.D., 1544 Cole Street, San Francisco 17, Calif.
Peyton, William T., M.D., Ph.D., 64 Barton Avenue, S. E., Minneapolis 14, Minn.
Pfeiffer, Carroll A., Ph.D., Yale University School of Medicine, New Haven 11, Conn.
Pierce, William Wright, M.D., 417 Bewley Building, Lockport, N. Y.
Pincus, Gregory, Sc.D., Worcester Foundation, 222 Maple Avenue, Shrewsbury, Mass.
Pinsonneault, Germain, M.D., Institut du Radium, 4120 Ontario Street, E., Montreal, Quebec, Canada.
Pitts, Herman C., M.D., 68 Brown Street, Providence 6, R. I.
Pollia, Joseph A., M.D., 269 S. Lake Street, Los Angeles 4, Calif.
Pomeroy, Lawrence A., M.D., 952 Hanna Building, Cleveland 15, Ohio.
Popper, Hans, M.D., Hektoen Institute for Medical Research, 629 Wood Street, Chicago 12, Ill.
Porter, Keith R., Ph.D., The Rockefeller Institute for Medical Research, 66th Street and York Avenue, New York 21, N. Y.
Potter, Van Rensselaer, Ph.D., McArdle Memorial Laboratory, University of Wisconsin Medical School, Madison 6, Wis.
Prickett, Cavett O., D.V.M., Regional Poultry Research Laboratory, East Lansing, Mich.
Prigosen, Rosa E., M.D., 1469 53rd Street, Brooklyn, N. Y.
Prime, Frederick, M.D., 131 East 66th Street, New York 21, N. Y.

Q

Queen, Frank B., M.D., Presbyterian Hospital, Nineteenth at Gilpin, Denver, Colo.
Quick, Douglas, M.D., 350 Park Avenue, New York 22, N. Y.
Quigley, Daniel T., M.D., 107 S. 17th Street, Omaha, Nebr.

R

Reimann, Stanley P., M.D., Lankenau Hospital Research Institute, Girard and Corinthian Avenues, Philadelphia, Pa.
Rezek, Philipp, M.D., Jackson Memorial Hospital, 1700 N. W. 10th Avenue, Miami, Fla.
Rhoads, Cornelius P., M.D., The Memorial Hospital, York Avenue at 68th Street, New York 21, N. Y.
Rhoads, Ernest E., M.D., 200-201 Paramount Building, 920 E. McMillan Street, Cincinnati 6, Ohio.
Rhoads, Jonathan E., M.D., University of Pennsylvania, Philadelphia, Pa.
Riegel, Byron, Ph.D., Northwestern University, Evanston, Ill.
Rigler, Leo G., M.D., University Hospital, 412 Delaware Street, S. E., Minneapolis 14, Minn.
Riker, Albert J., Ph.D., University of Wisconsin, Madison 6, Wis.
Ritchey, Mary G., M.D., Barnard Free Skin and Cancer Hospital, Washington and Theresa Avenues, St. Louis 3, Mo.
Robinson, William L., M.D., Faculty of Medicine, University of Toronto, Toronto, Canada.
Roffo, Angelo H., M.D., Instituto de Medicina Experimental, 5481 Avenue San Martin, Buenos Aires, Argentina, S. A.
Rosahn, Paul D., M.D., 92 Grand Street, New Britain, Conn.
Rosenthal, Otto, M.D., University of Pennsylvania, Philadelphia, Pa.
Rous, Peyton, M.D., Sc.D., Rockefeller Institute, 66th Street and York Avenue, New York 21, N. Y.
Rusch, Harold P., M.D., McArdle Memorial Laboratory, University of Wisconsin, Madison 6, Wis.
Russell, Elizabeth S., Ph.D., Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Me.
Russell, W. L., Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Me.
Russell, William O., M.D., Santa Barbara Cottage Hospital, Santa Barbara, Calif.

S

Sala, Angelo M., M.D., Welfare Island, New York, N. Y.
Salter, William T., M.D., Yale University School of Medicine, 333 Cedar Street, New Haven 11, Conn.
Saphir, Otto, M.D., Michael Reese Hospital, 29th Street and Ellis Avenue, Chicago 16, Ill.
Saxton, John A., M.D., Snodgrass Laboratory, 1426 Carroll Street, St. Louis 4, Mo.
Scharnagel, Isabel M., M.D., Address unknown.
Scheele, Leonard A., M.D., National Cancer Institute, Bethesda 14, Md.
Scheffey, Lewis Cass, M.D., Jefferson Medical College, Philadelphia, Pa.
Schenken, John R., M.D., Nebraska Methodist Hospital, Omaha, Nebr.
Schiller, Walter, M.D., 1401 Lake Street, Evanston, Ill.
Schlenk, Fritz, Ph.D., M. D. Anderson Hospital for Cancer Research, University of Texas, Houston, Texas.
Schlumberger, Hans G., M.D., University of Pennsylvania School of Medicine, Philadelphia 4, Pa.
Schneider, Walter C., Ph.D., McArdle Memorial Laboratory, Madison 6, Wis.
Schram, Mildred W. S., Ph.D., Donner Foundation, Inc., Land Title Building, Philadelphia 10, Pa.
Schreiner, Bernard F., M.D., 231 Humboldt Parkway, Buffalo 8, N. Y.
Schrek, Robert, M.D., Veteran's Hospital, Hines, Ill.
Seecof, David P., M.D., 1970 Daly Avenue, Bronx 60, N. Y.
Seelig, Major G., M.D., 4954 Lindell Boulevard, St. Louis, Mo.
Selbach, Gustav, M.D., 48 N. Main Street, Canadaigua, N. Y.
Selle, Wilbur A., Ph.D., University of Texas Medical School, Galveston, Texas.
Selye, Hans, M.D., Ph.D., University of Montreal, Montreal, Canada.
Semken, George H., M.D., 16 W. 85th Street, New York 24, N. Y.
Shack, Joseph, Ph.D., National Cancer Institute, Bethesda 14, Md.
Shafer, Rudolph J., M.D., 163 East First Street, Corning, N. Y.
Shear, Murray J., Ph.D., National Cancer Institute, Bethesda 14, Md.
Sheehan, George L., M.D., New York State Institute for the Study of Malignant Diseases, 663 N. Oak Street, Buffalo 3, N. Y.

Shemin, David, Ph.D., College of Physicians and Surgeons, 630 West 168th Street, New York 32, N. Y.
Shimkin, Michael B., M.D., National Cancer Institute, Bethesda 14, Md.
Shrigley, Edward W., Ph.D., M.D., Yale University School of Medicine, New Haven 11, Conn.
Siekmann, Carl F., M.D., New York State Institute for the Study of Malignant Diseases, 663 North Oak Street, Buffalo 3, N. Y.
Silberberg, Martin, M.D., Snodgrass Laboratory of Pathology, 1428 Carroll Street, St. Louis 4, Mo.
Silberberg, Ruth, M.D., Jewish Hospital, St. Louis, Mo.
Simmons, Channing C., M.D., 205 Beacon Street, Boston, Mass.
Simonds, James P., M.D., Ph.D., Northwestern University Medical School, 303 E. Chicago Avenue, Chicago, Ill.
Simpson, Burton T., M.D., 108 Homer Avenue, Buffalo 16, N. Y.
Simpson, Walter M., M.D., Miami Valley Hospital, 134 Apple Street, Dayton 9, Ohio.
Simpson, William L., Ph.D., Barnard Free Skin and Cancer Hospital, 3427 Washington Avenue, St. Louis 3, Missouri.
Singher, Heron O., Ph.D., Ortho Research Foundation, Linden, N. J.
Slye, Maud, Sc.D., 5825 Drexel Avenue, Chicago, Ill.
Smith, Fern W., Ph.D., Yale University School of Medicine, New Haven 11, Conn.
Smith, George M., M.D., Pine Orchard, Conn.
Smith, Lawrence W., M.D., 10 East 75th Street, New York 21, N. Y.
Smith, Leon H., M.D., 467 Linwood Avenue, Buffalo 9, N. Y.
Solomon, Harold Arthur, D.D.S., New York State Institute for the Study of Malignant Diseases, 663 North Oak Street, Buffalo 3, N. Y.
Spencer, Roscoe R., M.D., National Cancer Institute, Bethesda 14, Md.
Spies, John W., M.D., 1405 Northwood Road, Austin, Texas.
Spies, Thomas D., M.D., University of Cincinnati, Burnet and Goodman Streets, Cincinnati, Ohio.
Sproul, Edith E., M.D., American University of Beirut, Beirut, Lebanon.
Sprunt, Douglas H., M.D., University of Tennessee Medical School, Memphis 7, Tenn.
Steele, Robert, Ph.D., McArdle Memorial Laboratory, University of Wisconsin, Madison 6, Wis.
Steiner, Paul E., M.D., University of Chicago, Chicago 37, Ill.
Stenstrom, Annette E., M.D., 1517 E. River Road, Minneapolis, Minn.
Stenstrom, Karl Wilhelm, Ph.D., University of Minnesota School of Medicine, Minneapolis, 14, Minn.
Stevenson, Holland N., M.D., 421 Huguenot Street, New Rochelle, N. Y.
Stewart, Fred W., Memorial Hospital, York Avenue at 68th Street, New York 21, N. Y.
Stewart, Harold L., M.D., National Cancer Institute, Bethesda 14, Md.
Stone, Robert S., M.D., University of California Hospital, San Francisco 22, Calif.
Stout, Arthur P., M.D., College of Physicians and Surgeons, 630 West 168th Street, New York 32, N. Y.
Stowell, Robert E., M.D., Washington University School of Medicine, Euclid Avenue and Kingshighway, St. Louis 10, Mo.
Straus, Reuben, M.D., Cedars of Lebanon Hospital, 4833 Fountain Avenue, Los Angeles 27, Calif.
Strong, Leonell C., Ph.D., Yale University School of Medicine, 333 Cedar Street, New Haven 11, Conn.
Sugiura, Kanematsu, A.M., D.M.Sc., Old Memorial Hospital, 2 West 106th Street, New York 25, N. Y.
Suntzeff, V., M.D., Washington University School of Medicine, 640 S. Kingshighway, St. Louis 3, Mo.
Sutton, Richard L., Jr., M.D., 1115 Grand Avenue, Kansas City 6, Mo.
Swan, John M., M.D., 457 Park Avenue, Rochester 7, N. Y.
Swenson, Paul C., M.D., Jefferson Hospital, Philadelphia 7, Pa.
Syverton, Jermone T., M.D., University of Rochester School of Medicine and Dentistry, 260 Crittenden Boulevard, Rochester 7, N. Y.

T

Taffel, Max, M.D., Yale University School of Medicine, New Haven 11, Conn.
Tannenbaum, Albert, M.D., Michael Reese Hospital, 29th & Ellis Avenue, Chicago 16, Ill.
Tavares, C. A., M.D., 2120 Tuolumne Street, Fresno, Calif.
Taylor, Alfred, Ph.D., University of Texas, Austin, Texas.
Taylor, Howard C., Jr., M.D., 842 Park Avenue, New York, N. Y.
Taylor, Kenneth, M.D., 14 Sutton Place, South, New York 22, N. Y.
Thibaudeau, Alphonse A., M.D., New York State Institute for the Study of Malignant Diseases, 663 N. Oak Street, Buffalo 3, N. Y.
Thomas, Walter S., M.D., Monroe County Hospital, 435 East Henrietta Road, Rochester 7, N. Y.
Toennies, Gerrit, Ph.D., Lankenau Hospital Research Institute, Girard and Corinthian Avenues, Philadelphia 30, Pa.
Toth, Benedict J., M.D., 1907 West State Street, Olean, N. Y.
Traut, H. F., M.D., University of California Hospital, San Francisco 22, Calif.
Treves, Norman, M.D., 48 East 75th Street, New York, N. Y.
Truog, Clarence P., M.D., Ph.D., Address unknown.
Tullis, James Lyman, M.D., New England Deaconess Hospital, Deaconess Road, Boston, Mass.
Turner, Floyd C., M.D., "Ree-Turn"—Box 807, Boulder Creek, Calif.
Twombly, Gray H., M.D., Memorial Hospital, York Avenue at 68th Street, New York 21, N. Y.
Tyzzer, Ernest E., M.D., Sc.D., 175 Water Street, Wakefield, Mass.

V

Van Dyke, John H., Ph.D., Washington University School of Medicine, Euclid Avenue and Kingshighway, St. Louis 10, Mo.
Visscher, Maurice B., M.D., University of Minnesota Medical School, Minneapolis 14, Minn.
Voegtlin, Carl, Ph.D., University of Rochester School of Medicine and Dentistry, Rochester 7, N. Y.
Von Haam, Emmerich, M.D., Ohio State University College of Medicine, Neil and 11th Avenues, Columbus, Ohio.

W

Walker, Irwin M., M.D., 653 Main Street, Niagara Falls, N. Y.
Waltman, Charles A., M.D., Address unknown.
Warner, Stanley G., M.A., State Institute for the Study of Malignant Diseases, 663 N. Oak Street, Buffalo 3, N. Y.
Warren, Shields, M.D., New England Deaconess Hospital, 195 Pilgrim Road, Boston, Mass.
Warren, Stafford L., M.D., 500 Delaware Avenue, Oak Ridge, Tenn.
Wehr, William H., M.D., 739 Starin Avenue, Kenmore, N. Y.
Weiss, Emil, M.D., Ph.D., Northwestern University Medical School, 303 East Chicago Avenue, Chicago, Ill.
Weller, Carl V., M.D., University of Michigan Medical School, Ann Arbor, Mich.
Wells, Arthur H., M.D., St. Lukes Hospital, 915 East First Street, Duluth 5, Minn.
White, Edward Philip, M.D., Ph.D., Address unknown.
White, Florence Roy, Ph.D., National Cancer Institute, Bethesda 14, Md.
White, Julius, Ph.D., National Cancer Institute, Bethesda 14, Md.
White, Thomas N., Ph.D., National Bureau of Standards, Washington 25, D. C.
Wicks, Lester F., M.S., Barnard Free Skin and Cancer Hospital, Washington and Theresa Avenues, St. Louis 3, Mo.
Widmann, Bernard P., M.D., 250 South 18th Street, Philadelphia 3, Pa.

WILLIAMS, GEORGE Z., M.D., Address unknown.
WILLIAMS, ROGER J., Ph.D., Sc.D., University of Texas, Austin 12, Texas.
WILLIAMS, W. LANE, Ph.D., University of Minnesota School of Medicine, Minneapolis 14, Minn.
WILSON, HUGH M., M.D., Yale University School of Medicine, New Haven 11, Conn.
WILSON, LOUISE PALMER, Ph.D., Wellesley College, Wellesley, Mass.
WINCHELL, A. VAUGHN, M.D., American Oncologic Hospital, 3234 Powelton Avenue, Philadelphia, Pa.
WINER, LOUIS H., M.D., 416 N. Bedford, Beverly Hills, Calif.
WINTERNITZ, MILTON C., M.D., Yale University School of Medicine, 333 Cedar Street, New Haven 11, Conn.
WINZLER, RICHARD J., Ph.D., University of Southern California School of Medicine, Los Angeles, Calif.
WIRTH, JOHN E., M.D., Clinton Laboratories, Knoxville, Tenn.
WOGLOM, WILLIAM H., M.D., 621 Tilden Avenue, Teaneck, N. J.
WOLBACH, SIMEON B., M.D., Harvard Medical School, 25 Shattuck Street, Boston, Mass.
WOLFE, JACK M., Ph.D., Albany Medical College, 47 New Scotland Avenue, Albany, N. Y.
WOMACK, NATHAN A., M.D., 4500 Olive Street, St. Louis 8, Mo.
WOOD, DAVID ALVRA, M.D., Stanford University School of Medicine, 2398 Sacramento Street, San Francisco, Calif.
WOOD, FRANCIS C., M.D., Sc.D., St. Lukes Hospital, Amsterdam Avenue and 113th Street, New York 25, N. Y.
WOOLLEY, GEORGE W., Ph.D., Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Me.
WRIGHT, ARTHUR W., M.D., Albany Medical College, 47 New Scotland Avenue, Albany, N. Y.
WYETH, GEORGE A., M.D., Dodge Lake, New York 63, N. Y.

Z

ZAHL, PAUL ARTHUR, Ph.D., The Haskins Laboratories, 305 East 43rd Street, New York 17, N. Y.
ZAMECNIK, PAUL C., M.D., Massachusetts General Hospital, Boston, Mass.
ZECKWER, ISOLDE T., M.D., University of Pennsylvania Medical School, Philadelphia, Pa.
ZIMMERMAN, HARRY M., M.D., Montifiore Hospital, New York, N. Y.

Abstracts

Reports of Research

Induction of Sarcoma of the Liver in the Rat with Methylcholanthrene and Benzpyrene. EISEN, M. J. [Coll. of Physicians & Surgeons, Columbia Univ., New York, N. Y.] *Cancer Research,* **6**:421-425. 1946.

Sarcoma of the liver in the rat was produced in 7 of 27 animals that survived 248 days, the time required for the induction of the earliest tumor, after intrahepatic implantation of paraffin pellets containing 1 mgm. of methylcholanthrene or benzpyrene, or of cotton threads impregnated with 0.8 mgm. methylcholanthrene. Subcutaneous tumors were produced with pellets containing the carcinogens in 10 of 14 animals with a minimal latent period of only 119 days. This would suggest that the liver is less sensitive to the chemicals, but not completely refractory as has been reported by several investigators.—Author's abstract.

The Production of a Carcinogenic Agent in the Degradation of Cholesterol to Progesterone. BISCHOFF, F., and RUPP, J. J. [Santa Barbara Cottage Hosp. Research Institute, Santa Barbara, Calif.] *Cancer Research,* **6**:403-409. 1946.

Progesterone, in the amount and under the conditions that inhibited mammary cancer formation in strain RIII mice, failed to do so in Marsh-Buffalo mice. Ovariectomized Marsh-Buffalo mice that received 10 mgm. of progesterone per mouse subcutaneously over a 6 months period failed to develop mammary tumors; 3 mgm. of progesterone administered subcutaneously, alone or in combination with 500 units of estrone, failed to effect the development of the mammary glands of Marsh-Buffalo female mice. Mice receiving sesame oil containing crude progesterone contaminated with cholestenone, or containing the equivalent of cystalline cholestenone, developed oleomas at the site of injection. Crystalline cholesterol or progesterone under the same conditions was without influence. A crude synthetic progesterone, made by the method of Spielman and Meyer, resulted in a 32% incidence of malignant tumors at the site of injection compared with a 0% incidence in controls and a 1 to 2% incidence in the colony.—Author's abstract.

A Measure of the Stimulating Effect of Simple Injury Combined with Carcinogenic Chemicals on Tumour Formation in Mice. PULLINGER, B. D. [Labs. of Imp. Cancer Research Fund, London, England] *J. Path. & Bact.,* **57**:477-481. 1945.

Multiple simple excisions from mouse skin treated with large or small doses of benzpyrene stimulated the formation of tumors to approximately 2 to 3 times the number obtained in susceptible mice from which only one excision was made.—A. H.

Studies on the Effects of Radioactive Sodium and of Roentgen Rays on Normal and Leukemic Mice. EVANS, T. C., and QUIMBY, E. H. [Columbia Univ., New York, N. Y.] *Am. J. Roentgenol.,* **55**:55-66. 1946.

The effects of radioactive sodium and of whole body roentgen irradiation on white mice have been compared. Results of reduction in the number of white and red blood cells and in shortening the life span are similar for the two types of radiation. Mice with enlarged nodes and extremely high leukocyte counts were found especially sensitive to the radio-sodium. They were not tested with roentgen rays. The marked response was apparently due to radiosensitivity of the abnormal leukocytes rather than to any selective concentration of the material in lymph nodes.—E. H. Q.

The Histologic Effects of Radiophosphorus on Normal and Lymphomatous Mice. GRAFF, W. S., SCOTT, K. G., and LAWRENCE, J. H. [Univ. of Calif., Berkeley, Calif.] *Am. J. Roentgenol.,* **55**:44-54. 1946.

Hematological and histological studies on normal and lymphomatous mice which have been given radiophosphorus revealed characteristic effects on the hematopoietic tissues. Although a few animals recovered from generalized lymphomatosis after treatment with P^{32}, no evidence of any increased radiosensitivity of the neoplastic cells was observed. The limiting factors in the use of roentgen irradiation and P^{32} in the therapy of leukemia and allied diseases are discussed. —E. H. Q.

Restropin Factor in Cancer in Relation to the Reticulo-Endothelial System. CONNELL, H. C., MUNRO, L. A., and MEDLEY, A. [Hendry-Connell Research Foundation, Kingston, Ont.] *Canadian M. A. J.,* **54**:161-164. 1946.

It has been concluded by many that the body function responsible for resistance is resident in the reticulo-endothelial system (R. E. S.). The activity of the R. E. S. is indicated by the elimination of a dye-like congo red when injected into the blood stream (congo red index, C. R. I.). A number of workers have found an impairment of the R. E. S. in cancer as shown by histological examinations paralleled by C. R. I. determinations. There has been reported the recovery of two separate factors in alkaline extracts of the anterior lobe of the pituitary called positive and negative restropin. A positive restropin factor was found in the blood of normal, cancer-free animals whereas a negative factor was obtained from the blood of animals with Walker sarcoma. These findings were also obtained in human beings.

Microfilm copies of such papers here abstracted as are available may be obtained from Medicofilm Service of the Army Medical Library at 25¢ for each complete article, not exceeding 25 pages in length—and 10¢ for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittance may be made with subsequent orders and in such manner as found most convenient. Address—Medicofilm Service, Army Medical Library, Washington, D. C.

In the present report blood from 103 cancer patients were studied; 48% gave a negative factor, 34% a positive factor while 18% were neutral. The authors conclude that the whole idea of positive and negative restropin may be in error and now are studying the restropin problem from the standpoint of the effect of x-ray and non-specific substances on stimulation and depression of the R. E. S.—M. E. H.

A Microscopical Study of the Evolution of Mouse Mammary Cancer: The Effect of the Milk Factor and a Comparison with the Human Disease. BONSER, G. M. [Univ. of Leeds, Leeds, England] *J. Path. & Bact.,* **57**: 413-422. 1945.

In a study of the evolution of mammary cancer in the mouse, intra-acinous carcinoma is the first and most frequent form of cancer to be observed and is accompanied in a small number of cases by intraduct carcinoma. Studies of the effect of the milk agent have shown that it acts mainly upon the acini, leading to a high degree of acinous proliferation which progresses ultimately to intra-acinous and extra-acinous carcinoma. There is much variation in the degree of acinous hyperplasia preceding the initiation of the malignant process, but in general the greater this proliferation the more frequently cancer occurs. Extra-acinous or infiltrating carcinoma can be shown in nearly all cases to be preceded by intra-acinous carcinoma. In mice that have received estrogen but not the milk agent, a limit is set upon the growth process at the stage of hyperplasia. Thus the estrogen would appear to act as a developing factor upon breast tissue already sensitized by the milk agent.

There is a difference in the site of origin of mammary cancer in the mouse and in man. Intraduct cancer is far more common than primary intra-acinous cancer in the latter species. This observation raises the question as to whether a milk influence exists in the human subject and, if so, whether it has different tissue specificities. Nevertheless there are many points of similarity in the evolution of breast cancer in the two groups, as for example in both the orgin is frequently multicentric and the development gradual.—A. H.

An Experimental Approach to the Problem of Trauma and Tumours. PULLINGER, B. D. [Labs. of Imp. Cancer Research Fund, London, England] *J. Path. & Bact.,* **57**: 467-476. 1945.

Simple trauma in the form of a single excision of skin, combined with the previous application of a carcinogen, increased the chances of an animal developing a tumor by less than 1% when the carcinogenic stimulus was slight. However when a highly active carcinogen was used by itself the chances of tumor formation was increased 13%. —A. H.

Thymonucleic Acids in Human Tumors. STOWELL, R. E. [Washington Univ. Sch. of Med., and Barnard Free Skin and Cancer Hosp., St. Louis, Mo.] *Cancer Research,* **6**:426-435. 1946.

Twenty human tumors, including a leiomyosarcoma, a primary carcinoma of the liver, 5 epidermoid carcinomas, 2 transitional cell carcinomas, a basal cell carcinoma and 8 adenocarcinomas, were analyzed for their content of desoxyribose and ribose nucleic acids. The nucleic acids were measured in sections of tissue with a special photometric instrument consisting of a stable light source, filters, microscope, photocell, and amplification and recording apparatus. The relative amounts of desoxyribose nucleic acid in adjacent normal and neoplastic tissues were measuered by determining the absorption of monochromatic complementary light by Feulgen-stained material. Similarly, but less satisfactorily, the ribose nucleic acid was estimated by measuring the decreased staining with pyronine after treatment with ribonuclease enzyme. This photometric, histochemical method has the advantage that the exact cells being measured are visualized and identified as one type. The results were expressed as mean amounts per unit volume of tissue and per cell and can be compared with mean volumetric measurements of the cell, cytoplasm, nucleus, chromatin, nucleolus, and nuclear sap.

In 18 of the 20 tumors the amount of thymonucleic acid per unit volume and per cell was greater than in the adjacent homologous normal tissue. Statistical analysis showed that this increase per volume was significant in 11 instances and per cell in 9 tissues. Two-thirds of the tumors had more ribose nucleic acid per unit volume and per cell than the corresponding normal tissue. In half of the tumors this increase was more than 50%. A majority of the tumors had cells of smaller mean size with less cytoplasm. In most instances, the tumor cells had larger mean percentages of nuclear and chromatin material. Correlation coefficients show that the amounts of thymonucleic acid are larger in tissues having small cells and small masses of cytoplasm as well as cells with large percentages of nuclear and chromatin substance. In a total of 34 tissues analyzed to date by this method, no tumor has contained a statistically significant decrease in thymonucleic acid per unit volume. These results add further support to the theory that tumors have disturbances in their nucleoprotein and enzyme systems.—Author's abstract.

Mechanism of the Proteolytic Activity of Malignant Tissue Cells. FISCHER, A. [Biological Inst. Carlsberg Foundation, Copenhagen] *Nature, London,* **157**:442. 1946.

Rous sarcoma cells were grown in rabbit plasma and chick embryo extract throughout many passages without liquefaction of the medium occurring, but on transfer to homologous plasma, liquefaction occurred. The addition of fresh fowl serum to the rabbit-plasma medium induced liquefaction to the same extent as growth in chicken-plasma medium. When the fowl serum was first heated to 56° for 3 to 4 hours, however, liquefaction no longer took place, which suggests that proteolytic enzymes in the culture medium must play a fundamental part in digestion of the plasma clots by sarcoma cells. Confirmatory evidence was afforded by preparing cultures in rabbit plasma with the addition of rabbit serum which had previously been shaken with sand for half an hour. Following this, liquefaction of the plasma then took place as readily as if homologous plasma were used. Presumably, inactive proteolytic proenzymes present in the rabbit serum were activated by the shaking. It is suggested that both normal and malignant tissue cells are able on contact to activate proteolytic proenzymes in homologous blood plasma.—R. J. L.

Induced Antibodies That React *in vitro* with Sedimentable Constituents of Normal and Neoplastic Tissue Cells. Presence of the Antibodies in the Blood of Rabbits Carrying Various Transplanted Cancers. FRIEDEWALD, W. F., and KIDD, J. G. [The Rockefeller Inst. for Med. Research, New York, N. Y.] *J. Exper. Med.*, **82**:21-39. 1945.

Rabbit sera, of animals carrying either the Brown-Pearce carcinoma, the V2 carcinoma, the rabbit sarcoma I, or the Kato sarcoma, have been found to contain an antibody which will *in vitro* fix complement with extracts of various normal and neoplastic rabbit tissues. The portion of the extracts which react with the antibody are readily sedimentable in the high-speed centrifuge. The antibodies found in these rabbits differ from natural antibodies in that they are not found in normal rabbits and are stable for 30 minutes at 65° C.—D. S.

Incidence and Specificity of the Antibody for a Distinctive Constituent of the Brown-Pearce Tumor. MACKENZIE, I., and KIDD, J. G. [Rockefeller Inst. for Med. Research, New York, N. Y.] *J. Exper. Med.*, **82**:41-63. 1945.

Rabbits implanted with a Brown-Pearce carcinoma or injected with extracts of the carcinoma, developed an antibody which reacted specifically *in vitro* with a particular sedimentable fraction of an extract of the tumor. This constituent of the Brown-Pearce carcinoma differed immunologically from other sedimentable fractions which can be extracted from rabbit tissues. The results and implications of the study are discussed.—D. S.

The Heterologous Transplantation of Mouse Tumors Induced *in Vitro*. GREENE, H. S. N. [Yale Univ. Sch. of Med., New Haven, Conn.] *Cancer Research*, **6**:396-402. 1946.

The tumors induced *in vitro* by Dr. Wilton R. Earle of the National Cancer Institute have been successfully transplanted to guinea pigs and to mice of foreign strains. The ability to survive and to grow in animals of alien species identifies the tumors with the chemically induced and naturally occurring sarcomas, and adds further significance to their mode of origin.

The success of the transfer of the tumors to unrelated mice varied with the strain or species of the donor, and an examination of this relationship suggested that the stromal component of the tumor was concerned in the variation.—Author's abstract.

Multiple Malignant Growths. LOMBARD, H. L., LEVIN, M. L., and WARREN, S. *Cancer Research*, **6**:436-441. 1946.

Peller has suggested that a cured cancer protects against the development of other malignant neoplasms and has advocated the experimental induction of a skin cancer to prevent subsequent occurrence of the more fatal cancers of other organs, while Warren and his associates have presented data which indicate that the incidence of multiple primary cancers is sufficiently high to presuppose increased individual susceptibility. This paper, based on 5,078 records from the Massachusetts cancer clinics, suggests that individuals with skin cancers are predisposed to other skin cancers. There is also an indication that males with lip cancers have some predisposition to multiple skin cancers. There is no evidence that immunity to the formation of a second primary cancer is produced by the presence of cancer in any location.—Authors' abstract.

Physiological Studies on Tumor-Inhibiting Agents. II. Effect on Rectal Temperatures in Normal Rabbits of the *Serratia marcescens* Tumor-Necrotizing Polysaccharide of Shear. BECK, L. V., and FISHER, M. [Hahnemann Med. Coll., Philadelphia, Pa.] *Cancer Research*, **6**:410-420. 1946.

The *Serratia marcescens* tumor-necrotizing polysaccharide which Shear and his co-workers have brought to a high state of purity is extremely potent as a pyrogen when injected intravenously into rabbits. Measurable increases in rectal temperature occurred after injection of only 0.005 micrograms per kgm., and elevations of 2 to 3° C. were produced by 0.5 µgm. per kgm. and larger amounts. The fever reaction was intensified and prolonged on very warm days.

Death occurred within 24 hours in some of the rabbits given 20 to 100 µgm. per kgm. Rabbits that died usually exhibited a rather weak fever reaction, and greatly diminished muscular strength.

Elevation of the rectal temperature did not occur as long as the rabbit was tied down on a copper table, or cooled with ice water and cold air. It was possible to minimize the polysaccharide induced fever reaction using the following drugs in amounts that were not acutely toxic to the rabbit: antipyrene, isopropyl antipyrene, acetylsalicylic acid and di-allyl barbituric acid.—Author's abstract.

Clinical and Pathological Reports

Clinical investigations are sometimes included under Reports of Research

MULTIPLE TUMORS

Multiple Primary Tumors. HAYWARD, W. G. [Jamestown, N. Y.] *J. Urol.*, **54**:307-311. 1945.

This is principally a case report of an 82 year old male who in two years had these histologically proved neoplasms: (1) basal cell carcinoma of the perineum; (2) epidermoid carcinoma of the groin; (3) adenocarcinoma of the prostate; and (4) embryonal carcinoma of the testis.—V. F. M.

DIAGNOSIS

Delimitation of Subcortical Tumours by Direct Electrography. WALTER, W. G., and DOVEY, V. J. [Burden Neurol. Inst., Bristol, England] *Lancet*, **250**:5-9. 1946.

It has been shown by means of indirect electroencephalography that a space-occupying lesion has two effects on the electrical activity of the brain. (1) An indirect action due to edema, and vascular change, resulting in the production of delta waves. (2) Disappearance of all electrical activity when there is replacement of nervous

tissue by neoplasm, abscess, or hematoma. A needle electrode has been designed by which the electrical activity of the subcortical structures can be directly recorded. The details of the construction of the needle electrode and the technic for use are described. The results following the use of this needle have been clear and consistent although the appearance of the records depends upon whether or not a general anesthetic is being used. Normal cerebral white matter is identifiable by rhythmic electrical activity of the same type as that found in the cortex, while matter adjacent to a space-occupying lesion displays slow delta activity similar to that seen in the cortex in the same conditions. The presence of a space-occupying lesion can be detected by its electrical inactivity. From these facts it is possible to delimit with satisfactory precision the spacial extent of a subcortical lesion and the zone indirectly affected by it. The results of the investigations of 4 cases are described and discussed.—M. L.

Skin and Subcutaneous Tissues

Multiple Keloids Following Varicella. Thomas, E. W. P. *Proc. Roy. Soc. Med.*, **39**:229. 1946.

The patient, aged 14, was said to have had a severe attack of chickenpox 6 months ago. Many of the lesions became pustular and healed leaving numerous hypertrophic keloidal scars.—E. L. K.

Angioma Serpiginosum (Crocker). Wigley, J. E. M. *Proc. Roy. Soc. Med.*, **39**:89. 1945.

Description of a case.—E. L. K.

Breast

Bilateral Carcinoma of the Breast. Whigham, J. R. M. [St. Andrew's Hosp., London, England] *Brit. J. Surg.*, **31**:303-304. 1944.

Both breasts showed solid acinar polygonal cell carcinoma.—E. L. K.

Female Genital Tract

Arrhenoblastoma of the Ovary. Report of Two Cases. Goldstine, M. T. [Chicago Gynecological Society, Regular Meeting Nov. 16, 1945] *Proc. Inst. Med. Chicago,* **16**: 75-76. 1946.

The pathologic diagnosis in the first case was an undifferentiated arrhenoblastoma and in the second a highly differentiated tumor (testicular adenoma of Pick).—M. E. H.

A Granulosa Cell Tumour of Tubular or Adenomatous Type. Dougal, D. [Univ. of Manchester, England] *J. Obst. & Gynaec. Brit. Emp.*, **52**:370-371. 1945.

A woman aged 22 who had suffered from continuous uterine hemorrhage for 17 months was found to have a tumor of the right ovary composed of well-formed tubules lined by a single layer of cylindrical cells. There were large amounts of lipid in the inner portions of the cells and in the lumina.—E. L. K.

Total Abdominal Hysterectomy. A Study of 500 Cases. Danforth, W. C. [Chicago Gynecological Society, Regular Meeting Oct. 16, 1945] *Proc. Inst. Med. Chicago,* **16**: 75. 1946.

This study comprises a series of patients upon whom operations were performed. The indication for operation in 319 cases was myoma. Among the other principle indications for surgery were adenomyosis, carcinoma of the corpus, endometriosis, cervical lesions in which the cervix was definitely unhealthy, and sarcoma of the uterus which occurred only once.—M. E. H.

Male Genital Tract

Benign Intrascrotal Tumors. Morehead, R. P. [Bowman Gray Sch. of Med., Wake Forest Coll., Winston-Salem, N. C.] *Urol. & Cutan. Rev.*, **48**:592-597. 1944.

A review of the literature with discussion.—V. F. M.

Bilateral Orchiectomy in Advanced or Recurring Carcinoma of the Bladder With Severe Subjective Symptoms. A Preliminary Report. Shivers, C. H. de T. [Atlantic City Hosp., Atlantic City, N. J.] *J. Urol.*, **54**:539-546. 1945.

The two interesting cases of bladder cancer resistant to treatment, reported here, showed considerable relief from symptoms following bilateral orchiectomy. In one of these there was apparent retardation of growth locally and marked improvement in general condition during the 3 year follow-up period.—V. F. M.

A Biological Interpretation of Carcinoma of the Prostate and Its Significance. Angrist, A., and Khoury, E. N. [Queens General Hosp., Jamaica, N. Y.] *Urol. & Cutan. Rev.*, **48**:577-580. 1944.

A relationship between the histological appearance of the removed testis and the clinical results obtained by orchiectomy in cancer of the prostate could not be demonstrated. Also there was no connection between the presence or absence of vas deferens obstruction and the degree of tumor activity. "Five percent of all men over the age of sixty develop clinical carcinoma of the prostate" but the histological incidence is much greater.—V. F. M.

Urinary System

Massive Renal Fibrolipoma: Report of Two Cases. Tahara, C., and Hess, E. [St. Vincent's Hosp., Erie, Pa.] *J. Urol.*, **54**:107-115. 1945.

One tumor was intrarenal and the other was extracapsular. Both were considered benign. Both patients had hypertension which decreased after surgery.—V. F. M.

Wilm's Tumor With Adenocarcinoma of the Kidney in an Adult. Oesterlin, E. J. [Orangeburg, N. Y.] *Urol. & Cutan. Rev.*, **49**:731-734. 1945.

A case report with illustrations and discussion.—V. F. M.

Renal Adenoma: A Case Report. Strauss, A. [Cleveland, Ohio] *J. Urol.*, **54**:221-223. 1945.

A renal tubular adenoma 11 cms. in diameter was removed from a 49 year old female.—V. F. M.

Primary Carcinoma of Ureter with Special Reference to Hydronephrosis. Lazarus, J. A., and Marks, M. C. [New York, N. Y.] *J. Urol.*, **54**:140-157. 1945.

This is a good review covering 183 cases collected from the literature and the authors' experience. Forty-two per cent of the cancers were non-papillary. Men were affected

almost twice as frequently as women. The greatest incidence was in the sixth and seventh decades. Metastases were common. Treatment of choice is nephro-ureterectomy.—V. F. M.

Leiomyosarcoma of the Kidney: Report of Two Cases. Tetelman, M. M., and Lisa, J. R. [City Hosp., New York, N. Y.] *J. Urol.*, **54**:224-226. 1945.

A description of two cases with autopsies.—V. F. M.

Primary Carcinoma of the Ureter. Bowie, C. F., and Bors, E. [Hammond General Hosp., Modesto, Calif.] *J. Urol.*, **54**:434-437. 1945.

The authors add one case to the 175 previously reported. —V. F. M.

End Results in the Treatment of Bladder Tumors. Parmenter, F. J. [Buffalo General Hosp., Buffalo, N. Y.] *Urol. & Cutan. Rev.*, **49**:676-680. 1945.

This is a statistical study. Of 39 cases of papilloma seen from 1916 to 1932, "Six are known to be well." Of 46 cases of papillary carcinoma, "Four are apparently well; four others reported themselves well in 1935 and cannot be traced at this time." Of 25 cases with carcinoma one lived 23 years, 4 others died many years later without cancer, and the remainder died of cancer. Statistical observations on a similar group from 1933 to 1944 are presented in tables, the follow-up period being less than a year for many cases. In commenting on the "Papillary Carcinoma" group the author states: "The results are indeed depressing." Radiation by radon seeds or radium plaque gave the best results in recurring papillomas, papillary carcinomas, and carcinoma—simple fulguration being advised first for simple papilloma. X-ray and resection were disappointing.—V. F. M.

Tumors of the Urinary Drainage Tract: Urothelial Tumors. Melicow, M. M. [Columbia Univ. Coll. of Physicians & Surgeons, New York, N. Y.] *J. Urol.*, **54**:186-193. 1945.

This is principally a review of histology, but the author also considers the problem concerning why vesical tumors are not associated with other growths in the urinary tract, since the histologically similar pelvic neoplasms are quite often associated with other tumors in the ureter and bladder. A possible explanation is given in that a carcinogenic agent might be excreted in the urine and this acts at the site of longest contact or stagnation—the bladder.—V. F. M.

Sacrococcygeal Teratoma in an Infant of Five Months Causing Acute Urinary Obstruction. Woodruff, S. R., and Begner, J. A. [Bayonne Hosp., Bayonne, N. J.] *J. Urol.*, **54**:177-181. 1945.

The incidence in infants is about 3 times greater in females than males. The authors' case is described and illustrated.—V. F. M.

Oral Cavity

Recent Advances in the Treatment of Carcinoma of the Mouth and Jaws. Somervell, T. H. [London Mission Hosp., Neyyoor, Travancore, S. India] *Brit. J. Surg.*, **32**:35-43. 1944.

A review is presented based upon 20 years experience in a large Mission Hospital in Travancore, South India. Here epitheliomas of the tongue, jaws, teeth and lips occur more frequently than any other type of cancer.—E. L. K.

Intrathoracic Tumors

Multiple Cavernous Haemangiomas of the Lungs Successfully Treated by Local Resection of the Tumours. Janes, R. M. [Toronto, Canada] *Brit. J. Surg.*, **31**:270-272. 1944.

Hemangiomas were removed from both lungs at two operations. The patient had also hemangiomas on the lower lip. Such conditions of the lung "can be treated successfully by local resection of individual tumors providing none of the lesions are too massive, in which case a lobectomy or pneumonectomy would be preferable. Because of the danger of fatal haemorrhage, operation should not be delayed."—E. L. K.

Miniature Scar-Carcinoma of the Lung and the "Upper Sulcus Tumour" of Pancoast. Illtyd, J., and Pagel, W. [Central Middlesex County Hosp., Acton Lane, London, England] *Brit. J. Surg.*, **32**:85-90. 1944.

Two cases are described of primary squamous-cell carcinoma originating in the apical part of the pleural cavity and invading the ribs and vertebrae. Although both tumors appeared to be intrapulmonary in origin they belong to an unusual group presenting characteristic clinical, radiological and histological features. "We agree, therefore, with Pancoast that they deserve to be more widely known as a special entity, and we suggest that 'miniature scar-carcinoma of the lung with involvement of the thoracic inlet' is more descriptive of the pathology than the more general term 'superior pulmonary sulcus tumour.' "—E. L. K.

Gastrointestinal Tract

Gastric Mucosal Atrophy and Carcinoma of the Stomach. Stout, A. P. [Presbyterian Hosp., New York, N. Y.] *N. Y. State J. M.*, **45**:973-977. 1945.

The author has accumulated a number of surgically resected stomach specimens which were all treated in the same fashion by opening along the greater curvature, pinning out on a cork board, fixing in Bouin's fluid, and then taking ten or more sections from different areas according to a definite plan. There were thus made available multiple sections from 150 stomachs, 50 with gastric carcinoma, 50 with gastric ulcer and 50 without ulcer or carcinoma but were removed because of duodenal ulcer. This material was studied to see if any further information could be elicited which would be of value in deciding whether or not morphological changes in the gastric mucosa could be regarded as precancerous.

It was found that mucosal atrophy may appear as early as the third decade and from then on with ever increasing frequency and extent in the succeeding decades of life. Moreover, in comparable groups of stomachs, mucosal atrophy was found in a larger number of instances and tended to be more widespread in those with cancer than in those without cancer. In attempting to find actual progression from altered mucosal glands, it was impos-

sible to tell when there was juxtaposition of carcinoma and mucosal glands whether the carcinoma was invading the glands or developing from their epithelial cells. In occasional stomachs with carcinomas, multiple sections from various areas failed to show any epithelial changes at all, while other stomachs without cancer showed only minimal changes.—J. L. M.

Sarcoma of the Stomach. Porritt, A. E., Hughes, K. E. A., and Campbell, R. J. C. *Brit. J. Surg.*, **31**:395-398. 1944.

A round-celled sarcoma, involving the whole of the lesser curvature from cardia to pylorus, was removed at operation.—E. L. K.

Neurofibroma: A Gastroscopic Report. Paul, W. D., and Chapman, D. W. [State Univ. of Iowa Coll. of Med., Iowa City, Iowa, and Baylor Univ. Coll. of Med., Houston, Tex.] *Am. J. Digest. Dis.*, **12**:258-260. 1945.

The symptoms caused by this lesion were long-standing, dull epigastric distress and syncope accompanied by tarry stools and hematemesis. A mass in the anterior wall of the stomach, having a smooth surface and even rounded contour, was seen on gastroscopy. Blood flowed from the surface. A subtotal gastrectomy was successfully performed. There is a photograph of the specimen and of a microscopic section.—E. E. S.

Gastric Schwannoma. Sanguily, J., and Blanco, F. L. [Havana, Cuba] *Surgery*, **17**:328-336. 1945.

Report of a case in a 58 year old woman, in whom this benign tumor of the neurogenic type reached such a large size that on roentgenographic examination it resembled a bezoar.—W. A. B.

Lymphosarcoma of the Stomach. Cardon, L., and Greenebaum, R. S. [Chicago, Ill.] *Am. J. Digest. Dis.*, **12**:339-344. 1945.

The outstanding features of the case presented were: fever, tender epigastric mass, palpable spleen, achlorhydria, occult blood in the stool, and a stomach that filled poorly with barium and had a persistent deformity. At operation a soft mass at the pylorus and antrum resembled a granuloma, while the fundus was stony hard. This proved at autopsy to be a reticulum-cell sarcoma. The symptoms are discussed in detail in relation to differentiation of this lesion from a gastric carcinoma.—E. E. S.

Adenocarcinoma of the Jejunum Arising Around Polyps. Cheney, G. P., and Mezey, C. M. [Tumor Clin. of Lawrence and Memorial Associated Hosps., New London, Conn.] *Connecticut M. J.*, **10**:23-24. 1946.

A case report. A hard mobile tumor 5 cm. in length, involving the midjejunum was found, on histologic study, to be an adenocarcinoma. Malignant growths of the small intestine are 36 times less frequent than those of the large bowel, but they occur with about equal frequency in all three divisions.—M. E. H.

Adenocarcinoma of the Jejunum Associated with Hyperplasia of the Parathyroid Glands and Generalized Osteoporosis. Mulligan, R. M. [Univ. of Colorado Sch. of Med. and Hosps., Denver, Colo.] *Arch. Path.*, **40**:182-186. 1945.

Case report.—J. G. K.

Leiomyoma of the Jejunum. Intermittent Melena of Fourteen Years Duration, and Fatal Hemorrhage. Hanno, H. A., and Mensh, M. [Grad. Hosp., Univ. of Pennsylvania, Philadelphia, Pa.] *Ann. Surg.*, **120**:199-206. 1944.

The chief manifestations of leiomyomas of the small bowel are enterorrhagia and intestinal obstruction. The diagnosis is often not made because the presence of a tumor in the small bowel is not considered. Failure to make a correct diagnosis roentgenographically may be due to the subserosal position of some tumors and superimposition of bowel shadows. Introducing barium through a tube directly into the small bowel is sometimes helpful. A case is presented with a history of melena at intervals for 14 years and previous gastroenterostomy with no change in the patient's course. It is pointed out that if a celiotomy, which was indicated in spite of negative roentgenograms, had been performed, the subserosal leiomyoma found at autopsy could have been removed.—W. J. B.

Carcinoma of Ampulla of Vater—Successful Radical Resection. Watson, K. [East Surrey Hosp., England] *Brit. J. Surg.*, **31**:368-373. 1944.

Description of a case.—E. L. K.

Peritonitis Following Malignant Obstruction of Sigmoid and Free Perforation: Report of Three Cases. Black, B. M., and Evert, J. A. *Proc. Staff Meet., Mayo Clin.*, **21**:137-142. 1946.

The authors report three cases in which the perforation was situated at or very near to the obstructing lesion. All three patients recovered. The ancillary use of chemotherapy was of great importance, since recovery before the advent of the sulfonamide drugs and penicillin was unusual.—J. L. M.

Late Invasion of the Bladder and Prostate by Carcinoma of the Rectum or Sigmoid. Oppenheimer, G. D. [Mt. Sinai Hosp., New York, N. Y.] *J. Urol.*, **54**:162-165. 1945.

A review of 50 consecutive autopsy records of cases with cancer of the rectum or sigmoid indicated that 21 had invasion of the bladder. Two clinical cases also described. —V. F. M.

Primary Anastomosis in Carcinoma of the Colon. Clute, H. M., and Kenney, F. R. [New England Baptist Hosp., and Massachusetts Memorial Hosps., Boston, Mass.] *New England J. Med.*, **233**:799-803. 1945.

In a series of 48 cases of resectable cancer of the colon, intestinal anastomoses were done in 34—in 27 as primary operations and in 7 as secondary (right colon) procedures—with a mortality of 3%. Mikulicz resection was done in 18 cases, with colostomy closure in 10, without closure in 8 cases; there was a mortality of 11%. The authors recommend that the Mikulicz operation in cancer of the colon be used only in cases in which it seems impossible to re-establish continuity of the intestine by direct intestinal anastomosis, or unwise to attempt it. They find that with careful preoperative preparation, including preliminary cecostomies as indicated, with meticulous surgical technic and with individualized postoperative treatment, most patients having cancer of the colon can be safely operated on by resection of the lesion and intestinal anastomosis, and propose this as the method of choice.—C. W.

Lymphosarcoma of the Bowel in Childhood. Cutler, G. D., Stark, R. B., and Scott, H. W., Jr. [Children's Hosp., and Harvard Med. Sch., Boston, Mass.] *New England J. Med.*, **232**:665-670. 1945.

A brief review of the subject, and a report on 4 cases of lymphosarcoma and 1 case of reticulum-cell sarcoma of the bowel, treated surgically at the Children's Hospital during the past 15 years. Although a very rare condition, lymphosarcoma makes up such a large proportion of cases of neoplastic disease of the bowel in childhood that it is justifiable to consider a neoplasm of the intestinal tract in an infant or child as lymphosarcoma until it is proved otherwise. Four of the 5 patients died, 2 with terminal lymphatic leukemia. Radical surgical extirpation and heavy x-ray therapy (employed in the surviving patient) are recommended as offering the best chance of cure.—C. W.

Primary Resection (Closed Anastomosis) of Rectal Ampulla for Malignancy with Preservation of Sphincteric Function. Together with a Further Account of Primary Resection of the Colon and Rectosigmoid and a Note on Excision of Hepatic Metastases. Wangensteen, O. H. [Univ. of Minnesota, Minneapolis, Minn.] *Surg., Gynec. & Obst.*, **81**:1-24. 1945.

General discussion.—J. G. K.

Evolution of Sphincter Muscle Preservation and Re-Establishment of Continuity in the Operative Treatment of Rectal and Sigmoidal Cancer. Bacon, H. E. [Temple Univ. Sch. of Med., Philadelphia, Pa.] *Surg., Gynec. & Obst.*, **81**:113-127. 1945.

General discussion, illustrated.—J. G. K.

Surgical Treatment of Carcinoma of the Rectum. Besser, E. L., Peterson, F. R., and Dulin, J. W. [State Univ. of Iowa Coll. of Med., Iowa City, Iowa] *J. Iowa M. Soc.*, **35**: 468-471. 1945.

This is a statistical study of 348 patients admitted to the University of Iowa Hospitals because of carcinoma of the rectum during the 7 year period from January 1, 1937 to January 1, 1944. One hundred and thirty-nine patients, or 43%, presented operable lesions. There follows a discussion of the type of operation used, the preoperative and postoperative care.—M. E. H.

Bone and Bone Marrow

Giant-Cell Tumor of the Occipital Bone with Increased Intracranial Pressure. Giffin, M. E., and Love, J. G. *Proc. Staff Meet., Mayo Clin.*, **20**:284-287. 1945.

Giant-cell tumors arising from the sphenoid and ethmoid bones of the skull have been reported fairly frequently. The authors report what they believe to be the second case of giant-cell tumor of the occipital bone and the first case of giant-cell tumor in which there were obvious signs of increased intracranial pressure.—J. L. M.

Cholesteatoma of the Petrous Bone. Pennybacker, J. [Nuffield Dept. of Surg., Oxford] *Brit. J. Surg.*, **32**:75-78. 1944.

Description of three cases.—E. L. K.

Benign Giant Cell Tumor of the Spine. Report of a Case Occurring in the Cervical Spine. Brock, E. H., and Bogart, F. B. [Medical Corps, Army of the United States] *Am. J. Roentgenol.*, **54**:512-518. 1945.

This is a case report, illustrated with roentgenograms and details of successful roentgen therapy.—E. H. Q.

An Unusual Case of Ewing's Sarcoma. Swenson, P. C., and Teplick, J. G. [Jefferson Hosp., Philadelphia, Pa.] *Radiology*, **45**:594-598. 1945.

A case of Ewing's sarcoma in a 2 year old girl is reported. The course of the disease was extremely rapid with every bone in the body involved within 2 months. Extensive calcification of arteries was observed.—R. E. S.

Isolated Myeloma in a Fourteen Year Old Boy. Kaufman, J. [City and Gouverneur Hosps., New York, N. Y.] *Am. J. Surg.*, **69**:129-132. 1945.

A report of a myeloma in a boy whose first cousin was known to have died of myelogenous leukemia is presented. This present patient has remained well for 4 years following surgical removal of the tumor from the occipital bone and x-ray therapy.—W. A. B.

Disarticulation of the Innominate Bone for Malignant Tumors of the Pelvic Parietes and Upper Thigh. Sugarbaker, E. D., and Ackerman, L. V. [Ellis Fischel State Cancer Hosp., Columbia, Mo.] *Surg., Gynec. & Obst.*, **81**:36-52. 1945.

General discussion, with presentation of 6 unselected cases.—J. G. K.

Benign Giant Cell Xanthoma of the Knee Joint. Foote, R. F., and Fett, H. C. *Am. J. Surg.*, **70**:234-236. 1945.

A case report.—W. A. B.

Thrombopenic Purpura Secondary to Multiple Myeloma. Report of a Case. Russell, H. K., and Jacobson, B. M. [U.S.N.R.] *U. S. Nav. M. Bull.*, **45**:967-970. 1945.

A case report.—C. W.

Leukemia and Hodgkin's Sarcoma

Eosinophilic Leukemia and Eosinophilia Leukemoides. Heerup, L. Report to Danish Path. Soc., Nov. 24, 1941; from abstr. in *Acta path. et microbiol. Scandinav.*, **19**: 313-315. 1942.

A report of a patient believed by the author to have had eosinophilia leukemoides, and a discussion of the differences between this disease and true eosinophilic leukemia.—M. H. P.

Case Reports of Barnes Hospital. Clinical and Postmortem Records Used in Weekly Clinicopathologic Conference at Barnes Hospital, St. Louis. Case 78. Wood, W. B. J. C., and Moore, R. A., Editors. [St. Louis, Mo.] *J. Missouri M. A.*, **42**:555-563. 1945.

Case 78 was one of Hodgkin's sarcoma involving the stomach, lungs, liver, spleen, and tracheobronchial and preaortic lymph nodes. The tumor had extended from the wall of the stomach to involve the body and tail of the pancreas. There were ascites, bilateral hydrothorax, and atrophy and fibrosis of the bone marrow.—M. E. H.

Carotid Body

Carotid Body Tumors. Dickinson, A. M., and Traver, C. A. [Albany Med. Coll., Albany, N. Y.] *Am. J. Surg.*, **69**: 9-16. 1945.

The literature on carotid body tumors is reviewed. The tumors are usually slow-growing, and benign in the first years of their growth, and tend to recur. The one constant symptom is a swelling at the level of the bifurcation of the carotid artery. There may be associated attacks of faintness due to carotid sinus irritation. These features are well demonstrated in the 2 new cases presented here. —W. A. B.

Carotid Body Tumour. Robin, I. *Proc. Roy. Soc. Med.*, **38**:621. 1945.

Description of a case.—E. L. K.

Tumor of the Carotid Body. Sowles, H. K. [Boston, Mass.] *New England J. Med.*, **233**:62-64. 1945.

A short review of the subject and case report.—C. W.

Neurofibroma of the Carotid Body. Goodsitt, E., and Sudimack, G. [Huron Road Hosp., East Cleveland, Ohio] *Am. J. Surg.*, **67**:131-133. 1945.

A case report.—W. A. B.

Adrenal

The Adreno-Sympathetic Syndrome with Transposition of Viscera. Broster, L. R., and McKeith, R. C. *Brit. J. Surg.*, **31**:393-395. 1944.

A male aged 29 who suffered from attacks of hypertension was found to have a tumor of the right adrenal. During manipulation of the tumor the blood pressure rose to 225/145, and dropped to 90/70 within ten minutes after the growth's surgical removal. The tumor, a pheochromoblastoma, was composed of large polyhedral cells giving a chromaffin reaction.—E. L. K.

Adrenal Virilism—Report of a Case with Unusual Features. McLetchie, N. G. B. *Brit. J. Surg.*, **32**:90-99. 1944.

The patient who had lived first as a female and then as a male, died from peritonitis. At the autopsy there was found: 1) mammary carcinoma with hepatic metastases; 2) bilateral ovarian dermoid cysts; 3) epithelioma arising in the right ovarian dermoid and invading the colon; 4) right adrenal represented by ridges of thickened cortex upon a calcified and ossified medulla.—E. L. K.

Bilateral Carcinoma of the Adrenal Cortex As a Cause of Severe Backache With Report of a Case. Zaslow, J., and Bernstein, M. [Jewish Hosp., Philadelphia, Pa.] *J. Urol.*, **54**:409-412. 1945.

Case report.—V. F. M.

Pancreas

The Surgical Treatment of Carcinoma of the Body of the Pancreas. Brunschwig, A. [Univ. of Chicago, Chicago, Ill.] *Ann. Surg.*, **120**:406-416. 1944.

After a review of the literature, 6 cases of carcinoma of the pancreas are reported. Resection of the body of the pancreas and the spleen was done in 4 cases and total pancreatectomy, duodenectomy, and splenectomy in 2. There was an immediate mortality of 50%, while the longest survival was 3 years and 11 months. An outline of the surgical procedures is included, and the importance of blood transfusions is stressed. Although the results may seem discouraging, there was postoperative relief of pain in 3 cases, and the present work is regarded as only one stage in the development of effective therapy.—W. J. B.

Back Pain as a Symptom of Carcinoma of the Body of the Pancreas. Kattwinkel, E. E. [West Newton, Mass.] *Ann. Int. Med.*, **23**:1006-1009. 1945.

A case report. Carcinoma of the pancreas should be suspected if indigestion is accompanied by a back pain that is worse when the patient lies down and is relieved when he bends forward.—J. G. K.

Spontaneous Hypoglycemia Due to Islet-Cell Tumors of the Pancreas. Clyne, R. M., Leeds, H. M., and Cowdery, J. S. [Lincoln Hosp., New York, N. Y.] *N. Y. State J. M.*, **45**:405-409. 1945.

The authors review the literature on islet-cell tumors and have collected 60 additional cases, 56 of which were benign, and 4 malignant. The physiology of hyperinsulinism is briefly discussed. In addition there is presented a summary of the more interesting cases in the literature of the past five years. This paper adds to the literature one islet-cell tumor, a benign adenoma. This brings a total of islet-cell tumors to 176. Of these 127 are benign adenomas, 27 carcinomas, and 22 questionable carcinomas. Two case reports are presented.—J. L. M.

Thymus

Malignant Thymoma. Wilson, F. N., and Pritchard, J. E. [Montreal Gen., Hosp. Montreal, Canada] *Canad. M. A. J.*, **53**:444-454. 1945.

The authors have attempted in a general way to clarify the problems of malignant thymoma by indicating its histogenic nature. The position of the two cell types, epithelial and lymphoid, in thymic oncology is discussed. Representative cases are presented.—M. E. H.

Miscellaneous

Endometriosis. Counseller, V. S., and Sluder, F. S. [Rochester, Minn.] *Rocky Mountain M. J.*, **42**:189-194. 1945.

The pathology, diagnosis, and surgical treatment of endometriosis are discussed, on the basis of 754 cases in which operation was performed between the years 1938 and 1941 for endometriosis of the genital, urinary, and digestive tracts, and various other parts of the body.—M. E. H.

The Incidence, Prognosis and Curability of Malignant Lesions. A Brief Review. Dixon, C. F. [Mayo Clin., Rochester, Minn.] *J. Iowa M. Soc.*, **35**:215-219. 1945.

The chances for cure after proper treatment are related directly to the extent and activity of the growth at the time treatment is started. The early recognition and diagnosis of cancerous growths and the guidance of public education are the duty of every qualified physician. —M. E. H.

The Impact of the Cancer Program on the Medical Profession. Creadick, A. N. [New Haven, Conn.] *Connecticut M. J.*, **9**:428-430. 1945.

The author predicts that renewed interest in the cancer program as well as the prospects of increased funds will touch the life and practice of every person in the medical profession. The service provided to the patient will make changes in our present clinic programs. The good ultimately will depend to a great degree on the efforts of the medical practitioner.—M. E. H.

Carcinoma in the Overseas Soldier. Judd, E. S. *Proc. Staff Meet., Mayo Clin.*, **20**:289-291. 1945.

A brief discussion of the problem is presented together with a report of a patient with carcinoma of the colon.—J. L. M.

Cancer in Cows' Udders Extremely Rare. [U.S.D.A. Research Admin., May 29, 1945] *J. Am. Vet. M. A.*, **107**:75. 1945.

Federal meat inspection service disclosed that there were 32,709 cattle in 1944 which were found to have tumors, many of them malignant, but none occurred in the udder. This is especially striking in view of the frequency of breast cancer in many other species.—E. E. S.

STATISTICS

Cancer Mortality and Marital Status; an Analysis of Deaths Attributed to Cancer Among the White Population of New York City During 1939-41. Duffield, T. J., and Jacobson, P. H. [Bureau of Records and Statistics, Dept. of Health, New York, N. Y.] *J. Nat. Cancer Inst.*, **6**:103-112. 1945.

The recorded deaths from cancer among the white population of New York City, 15 years of age or older, during the 3-year period 1939 through 1941, were analyzed with regard to marital status. The over-all mortality rate for cancer of all types and in all sites was slightly higher in the unmarried population both male and female. In the female population, cancer of the breast and genital organs other than uterus was more prevalent among spinsters, while uterine cancer occurred at a higher rate among married women. Of the tumors in the male, prostatic cancer resulted in a higher mortality rate in the married group, while cancer of the buccal cavity and pharynx had a 73% higher rate among single men. In the case of cancer of the stomach, the married group showed the higher rate, 5% for the males and 20% for the females. The mortality rates for cancer of the peritoneum and digestive tract (other than the stomach) and the respiratory system were not significantly different in the married and unmarried groups, although cancer of "other and unspecified organs" was slightly more prevalent in the unmarried group. Some of the implications of these statistics were discussed.—R. A. H.

The Susceptibility of Indians to Cancer. Khanolkar, V. R. [Tata Memorial Hosp., Bombay, India] *Indian J. M. Research*, **33**:299-314. 1945.

The information regarding the incidence of cancer in India has been very conflicting in the past. The author has, therefore, reviewed the clinical experience of trained observers from different parts of the country, as well as his own experiences covering 3,919 autopsies performed at the King Edward Memorial Hospital, Bombay, and clinical cases at the Tata Memorial Hospital. He has analyzed the official vital statistics after noting the limitations and shortcomings of such data in India. He finds that wherever reasonably accurate information is available the total incidence of cancer in India, Europe, and America shows very little difference; and that any apparent difference disappears when comparable age groups are considered. He further shows that even though there may be no racial difference regarding the total incidence of cancer in human beings, there exists a considerable difference in the incidence of separate forms of cancer, or of cancer of various parts of the body in the different peoples of India.—Author's abstract.

CANCER CONTROL AND PUBLIC HEALTH

Interim Report of the Joint Advisory Committee of the Cotton Industry. Mule Spinners' Cancer and Automatic Wiping-down Motions. Gt. Brit. Ministry of Labour and National Service. May 17, 1945.

A Committee was appointed to consider among other things (a) the prevention of mule spinners' cancer and (b) the provision of mechanical means of wiping-down the carriage tops and roller beams of the mules in order to eliminate manual methods. The Committee recommended (1) that the oils used for spinning mules should conform to certain specifications of refractivity and specific gravity (2) that devices be provided to prevent the splashing of oil from mule spindles (3) that a private medical examination be provided every 6 months for all persons engaged in mule spinning and (4) that mechanical means of wiping-down be provided as stated under (b) above.—E. L. K.

The Tumor Clinic. Its Function, Organization and Operation. Zimmerer, E. G. [Division of Cancer Control, Iowa State Dept. of Health, Des Moines, Iowa] *J. Iowa M. Soc.*, **35**:396-399. 1945.

The tumor clinics serve a humanitarian role by providing the best available treatment for the patients, and also give an opportunity to collect data on cancer. Furthermore they serve as important educational opportunities for physicians. The author urges more tumor clinics for Iowa.—M. E. H.

The Expansion of the Connecticut Cancer Program. Griswold, M. H. [Division of Cancer Research, Connecticut State Dept. Health, Hartford, Conn.] *Connecticut M. J.*, **10**:18-21. 1946.

At the present time there is scarcely a home in the State of Connecticut more than 25 miles from a cancer center. The percentage of individuals with cancer receiving treatment within 1 month of the first symptoms has steadily increased, and the number of individuals who received treatment within 4 or 6 months of this disease is also greater. Twenty-one hospitals in Connecticut have provided the facilities for the diagnosis and care of cancer patients. As of July 1945, 27 hospitals have complete registries, 3 others have partial registries, and the remaining will start this service as soon as time permits.—M. E. H.

Correction

Volume **6**:282 (Abstracts) 1946. Effects of Implantation of Methylcholanthrene in the Brain of the Dog, the second line "dogs provoked a chronic granulomatous reaction on the" was omitted.